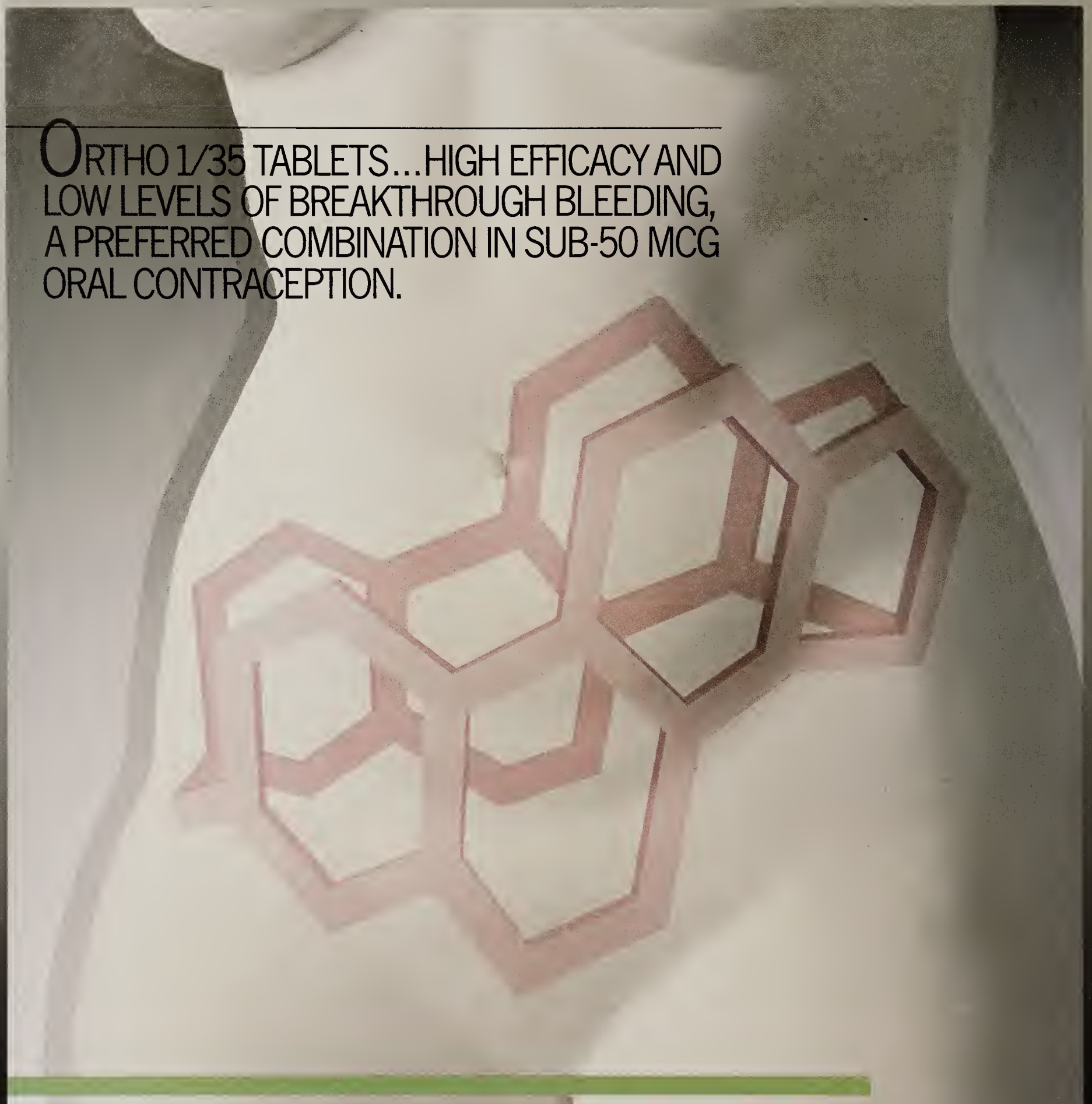
University of Toronto
Library - Serials Dept.
Campus

University of Toronto
MEDICAL JOURNAL
VOL LX *60th Anniversary* NO. 2

In this issue:

The Philosophy and Nature of Medical Research

by Dr. Robert Salter



ORTHO 1/35 TABLETS...HIGH EFFICACY AND LOW LEVELS OF BREAKTHROUGH BLEEDING, A PREFERRED COMBINATION IN SUB-50 MCG ORAL CONTRACEPTION.

1 mg norethindrone. The preferred progestin with minimal impact on lipid and carbohydrate metabolism.[1,2,3]

35 mcg ethinyl estradiol. A trusted estrogen at an effective and trusted level.

Combined to provide preferred performance. High efficacy shown with no pregnancies occurring in clinical trials when tablets were taken as directed.[4]

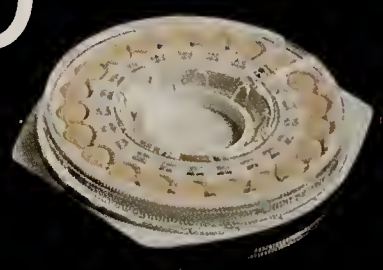
Low levels of breakthrough bleeding, closely approaching those of leading 50 mcg products.[4]

ORTHO* 1/35

ORTHO PHARMACEUTICAL (CANADA) LTD.
Don Mills, Ontario

ORTHO

1 mg norethindrone and
35 mcg ethinyl estradiol tablets



*Trademark ©Copyright 1982, Ortho Pharmaceutical (Canada) Ltd.
PAAB CCPP

P83-0092

University of Toronto
MEDICAL JOURNAL

Established 1923. An Undergraduate Publication — *60th Anniversary* — Volume LX, Number 2, January 1983

CONTENTS

Guest Article:
The Philosophy and Nature of Medical Research.
R.B. Salter, O.C. M.D., ...35

Orthopaedics:
The Anterior Cruciate Ligament — A Review.
J.T. Bertoia 39

Oncology:
Clinical and Pathological Aspects of Nasopharyngeal Carcinoma.
Andie Lam 42

Oncology:
Small Cell Lung Cancer Part II: A Case Presentation.
M.J. Bazos and W.K. Evans, M.D., F.R.C.P.(C) 48

Review Article:
Two Pathways of T-cell Mediated Immune Tolerance of the IgE System.
W. David Colby, M.Sc. 52

Book Review:
Living and Working with Schizophrenia.
Lora Lee Hamilton 56

Nutrition and Medicine:
Dietary Fiber and Colon Cancer: Is There a Link?
Ruth M. Kay, Ph.D. 58

The Final Word:
Notes from the Front: A Perspective of Creativity.
Harley Hahn 60

Editor ....Michael Dan 8T4

Advertising Director ....Michael Bazos 8T5

Executive Staff ....Dele Davies 8T5
Eric Grafstein 8T5
Lora Hamilton 8T5
Linda Harvey 8T5
Doug Kondiziolka 8T5
Liz Keay 8T5
Sal Sirna 8T5

Advisory Staff ....Davy Cheng 8T3
Paul Boughen 8T3

Editorial Page ....Harley Hahn 8T4

Art as Applied to Medicine ....Rhonda Legrove 8T4

Cover Illustration ....Elizabeth Gilbert 8T5

GUIDELINES FOR PUBLICATION

1) All articles intended for publication should be submitted to the editors before the deadline which is usually six weeks before the release of the Journal.
2) Submitted articles should be typed double-spaced, single sided on paper 8½"x11" (letter size) and they should not be more than 15 to 20 pages (3000 to 4000 words).
3) Illustrations, graphs, diagrams and figures should be put on a separate sheet and identified by Arabic numerals. A list of explanatory legends for all the figures and diagrams should be put on another sheet. Do not write on the back of photographs.
4) References should be checked with the original sources, designated by raised Arabic numerals in the text, and listed in alphabetical order on a separate sheet. Each periodical reference should include in order: the author's last name and initials, title of the article, journal name, volume number, page number, and year (e.g. Risser JC: Scoliosis: Past and Present. *J. Bone and Joint Surg* 46A:167, 1964). For further information please consult the MLA Stylesheet.
5) The editors reserve the right to make such editorial changes as are deemed necessary to ensure correctness of grammar and spelling, clarification of statement and conformity to Journal style.
6) Acceptance for publication is subject to the understanding that such material is submitted solely to the Journal and will not be reprinted without the consent of both the editors and author.

When you think quality drugs at moderate prices...

Some of our
quality pharmaceuticals:

Novo-Ampicillin	(Ampicillin)	**Novomedopa**	(Methyldopa)
Novocloxin	(Cloxacillin)	**Novosemide**	(Furosemide)
Novodipam	(Diazepam)	**Novotetra**	(Tetracycline)

Write for complete list of our pharmaceuticals. Widely dispensed by most hospitals and retail pharmacists. Prescribed by many doctors.

you think *novopharm*

THE LARGEST CANADIAN-OWNED COMPANY
SPECIALIZING IN PRESCRIPTION DRUGS.

1290 ELLESMERE ROAD, SCARBOROUGH, ONTARIO (416) 291-8876

GUEST ARTICLE

The Philosophy and Nature of Medical Research*

Robert B. Salter, O.C., M.D., M.S., F.R.S.C., F.R.C.S.(C), F.A.C.S.
Professor and Head of Orthopaedic Surgery, University of Toronto.

I am directing this article to *you* as a medical student because you have the potential to become a medical scientist or clinician-scientist — either part-time or full-time — and also because of my own personal conviction that research is essential to the continuing progress of all medical and surgical specialties.

My purpose is three-fold: first to help you to appreciate the importance and philsophy of medical research; second, to stimulate you to contemplate the possibility of your own personal involvement; and third, to share with you some thoughts concerning the *nature* of such research as well as some guidelines concerning the scientific method — thoughts and guidelines that I have found especially helpful during a 25 year period of consistent, part-time involvement in this fascinating and exciting facet of academic medicine.

For these purposes the terms "medical" and "medicine" are used in their broadest context in that they are meant to include all medical and surgical specialties within the profession even though I write from my perspective as an orthopaedic surgeon-scientist.

A Definition of Research

The English noun, *research*, is derived from the French verb "rechercher" which means simply to look again or to take a second look — in contradistinction to being satisfied with one superficial look. Thus, research involves taking a fresh and concentrated look at a given problem in an attempt to find a solution.

From a distillation of definitions in various dictionaries, *research* could be defined as "as investigation or experimental study of some phenomenon directed to the discovery and interpretation of new data through the critical approach of the scientific method."

The Image of Medical Research

As an undergraduate medical student of today, you may have been negatively influenced by the current trend among some of the young to harbour feelings of anti-establishment and anti-science. Added to this you will have heard much about the budgetary constraints on research funding through governments and also that there may be few opportunities for either full-time or part-time positions in medical research. Although such negative attitudes have often been exaggerated they may explain — at least in part — why only approximately 5% of undergraduate medical students in North America are currently attracted to a career in medical research.

This negative image of research, although unjustified, is not new for as the 19th Century philosopher and critic, John Ruskin wrote "Science lives only in quiet places, and with odd people, mostly poor." But all of that has changed! Visit the medical or surgical research laboratories in your own university and you will find them not to be "quiet places" but rather hives of intellectual and physical activity; you may find the medical or surgical scientists unusual or uncommon individuals perhaps, but not "odd" and you will find that they are no longer "mostly poor."

The Goals and Importance of Research

In the broad fields of medicine and surgery and their related basic sciences the primary goal of the various types of research is to achieve a more complete understanding of biological processes — both normal and abnormal — in order to make significant advances in the treatment of disorders and injuries in man through the development of more effective methods for their prevention, detection or treatment. In this sense, all medical research has a bearing on health — either directly or indirectly, either immediately or eventually.

In an academic setting, however, research has an additional goal, namely the enrichment of the *education* — as opposed to the mere *training* — of a clinician. In this context the term "education" implies the intelligent understanding of clinical teaching while the term "training" implies uncritical acceptance of such teaching.

Research enhances the quality of medical education — both undergraduate and postgraduate — because the scientific atmosphere has a beneficial impact on all aspects of the educational program and, in addition, such an atmosphere is testimony to the fact that medicine as a science is dynamic, growing and constantly changing for the better. Furthermore, a lively and exciting program of medical research in a given University attracts the brightest young people as postgraduate students and new faculty members to that University.

Through your personal involvement in either clinical or experimental investigation as an undergraduate or postgraduate student you should acquire qualities such as intellectural curiosity, critical thinking, logic and discrimination that can be applied not only to your own work but also the work of your colleagues as expressed through both the spoken and the written word. Indeed, in any postgraduate surgical training program that does not include a significant amount of research activity, the potential clinician will receive more of a technical or trade school training than a true medical education in both the art and science of Medicine.

In a given university the importance of medical research

* *A modified version of the author's article entitled "The Philosophy and Nature of Surgical Research" published in the Canadian Journal of Surgery 23(4): 349-354, 1980.*

varies directly with the degree to which these two major goals are being achieved. Although much more emphasis on medical research is required throughout the world, such research has already gained a position of great importance in many of our major universities not only because of its intrinsic contributions to new knowledge but also for its contributions to medical education.

First-rate medical research within a University Medical School invariably improves the quality of *patient care* in the affiliated teaching hospitals of that University — and indeed the quality of patient care in hospitals throughout the world — since new scientific knowledge is soon shared with fellow clinicians and scientists internationally through the media of scientific meetings and publications.

The Motivation for Search and Research

Search for knowledge that is both true and new has always challenged and motivated intelligent humans. In his famous 12th Century Prayer the physician-philosopher Maimonides expressed such motivation thusly, "Let the thought never arise that I have attained to enough knowledge."

One of the world's leaders in the philosophy of science, Karl Popper, has stated that "It is not the possession of knowledge, or irrefutable truths, that constitute the man of science, but the incessant search for truth."

The underlying motivation of the scientist to become engaged in research — and indeed wedded to it — is a combination of intellectual curiosity and dissatisfaction with the current state of knowledge and understanding. As Voltaire has said "Without the spirt of *constructive discontent* we would still be eating acorns and sleeping under the stars."

The Philosophy of Medical Research

Inherent in the philosophy of research, is the aforementioned "constructive discontent" with the existing state of knowledge and traditionally accepted — but unproven — concepts. And yet as an undergraduate medical student you will have acquired an incredible amount of cognitive information, at least some of which needs to be challenged. George Perkins, a distinguished British orthopaedic surgeon who dared to differ with his more traditionally-minded contemporaries once stated that "The training of a medical doctor is such that it is difficult for him to break with tradition" — a sad commentary relevant to the difference between "training" and "education."

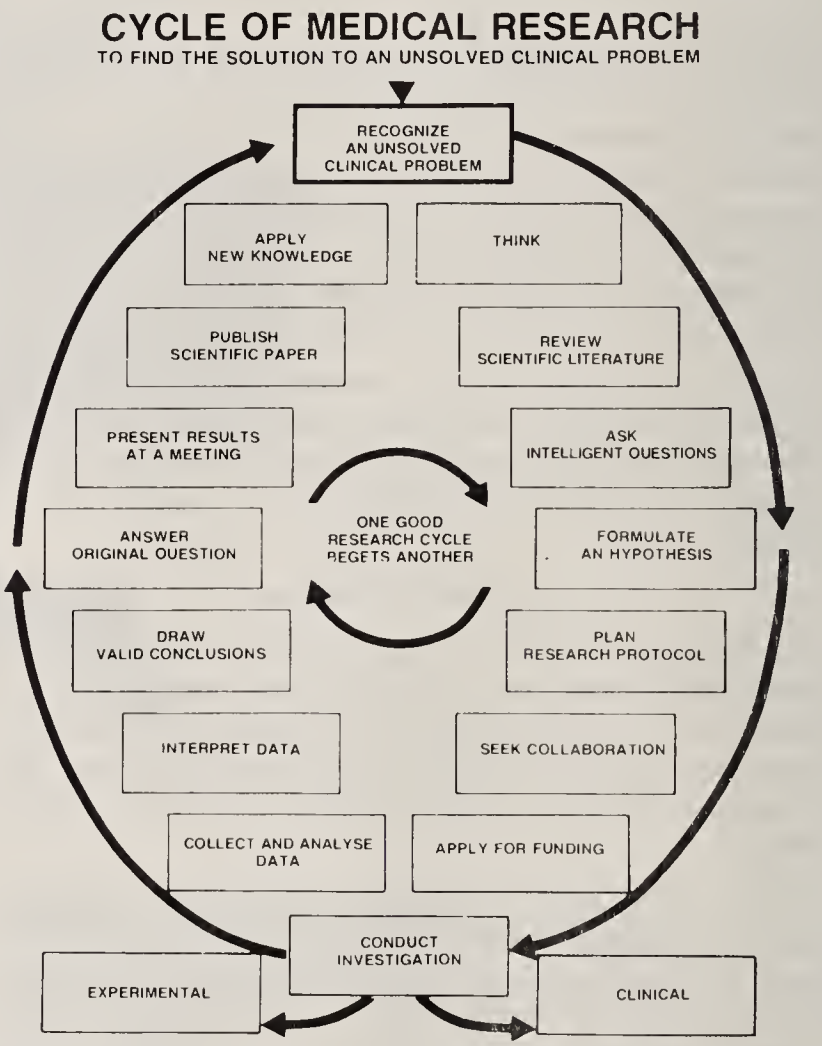
Although the success of research depends upon many factors, the pivotal and initiating factor is the scientific curiosity of the investigator, a curiosity that compels him or her to discover — or uncover — new data and new concepts through the application of the scientific method.

Understandably, the life of the clinician-scientist is not easy but it can be very rewarding in terms of the quiet satisfaction that comes from achieving a scientific goal. In a sense the clinician-scientist is a bridge-builder who constantly strives to bridge the gap between the practical art and theoretical science of medicine. To be effective in this role the medical scientist must merit the respect of both fellow clinicians and fellow scientists and this calls for exemplary performance in *both* fields.

The Nature of Medical Research - A Cycle

Even the most inspired and idealistic of potential scientists must accept and work within the rigorous discipline of the scientific method, the essence of all research. seemingly complex and formidable at first to the uninitiated or inexperienced, the scientific method is best understood if presented as a series of well planned phases or steps.

During many years of teaching and supervising both undergraduate and postgraduate research fellows, I have found the concept of what one might call the "cycle of medical research" to be most helpful in outlining and explaining the multiple phases of the time-honoured scientific method (Fig. 1) The cycle consists of a series of guidelines that start with patients and come back to patients because medical research of the mission oriented or targeted type is designed to find the solution to an unsolved clinical problem in patients and in due course, whenever appropriate, to apply the new found knowledge to that problem.



In this cycle of medical research there are 16 phases each of which merits your individual attention.

1. Recognize an Unsolved Clinical Problem

In order to find a solution to a given unsolved clinical problem it is essential that as a clinician-scientist you first *recognize* that problem or a component of it and this involves being a keen and alert observer — a human biology watcher. Unfortunately a pure clinician may "have eyes but see not" and may miss the critical observation that would lead to recognizing an unsolved clinical problem and to its investigation. "In the field of observation", wrote Louis Pasteur, "chance favours the prepared mind."

2. Think

To *think* deeply, contemplatively and speculatively about an unsolved problem requires determination and self-discipline on your part since there are so many interruptions in the daily — and even nightly — life of a physician or surgeon. Furthermore, such thinking is more difficult and more taxing than, say, making a fairly obvious diagnosis, prescribing a routine medical regimen or performing a routine surgical operation. It may, however, bring its own rewards such as the intellectual exhilaration that results from successful problem-solving.

3. Review the Scientific Literature

Before embarking on any research project you will need to review the scientific background against which your work will stand. In medical research as in other forms of research there have been many examples of "rediscovering the round wheel" which could have been avoided had the investigator been aware of the historical background of the subject. Churchill and others have expressed the thought that those who do not read history are doomed to repeat the errors (and one might add, the experiments) of the past. Fortunately literature surveys have been tremendously facilitated by modern computerized library science. As you review the scientific literature relevant to the problem that you have recognized, you will not only be able to benefit from the labours of fellow scientists but you will also be stimulated to build upon such labours through your own original thinking and questioning.

4. Ask an Intelligent Question

Having read the historical background of the problem you then need to ask an intelligent question, and furthermore, a question that can be feasibly answered through research. In relation to a specific phenomenon under investigation the question frequently begins with why? how? what? or which? Much time, effort and money will be wasted if an inappropriate question forms the underlying basis for a research project for as the scientist Sir Henry Tizard has emphasized "The secret of success in science is to ask the right question."

5. Formulate an Hypothesis

As the first step toward answering your own question you should formulate an hypothesis (literally a subordinate thesis or a theoretical and provisional supposition which serves as a starting point for further investigation by which it may be proved or disproved). The working hypothesis is a carefully reasoned but as yet unproven answer to the question and should lend itself to the testing of its validity through the research project that is being planned.

6. Plan the Research Protocol

The next step in the *cycle of surgical research* is to plan in detail the *protocol*, or strategy, of the investigation, that is, the experimental design, including the subjects of the investigation (either animals or human patients), the investigational methods, the equipment, the "controls" to deal with all possible variables and finally the proposed methods of analysis of the data including the determination of statistical significance. The protocol should be planned with the primary purpose of the investigation in mind, namely the testing of the validity of your hypothesis.

7. Seek Collaboration

As biomedical research becomes increasingly complex and sophisticated, you *must* be prepared to collaborate with scientists of other disciplines — such as physiology, biochemistry, microbiology, immunology, biophysics and biomedical engineering — in multidisciplinary research. Through such collaborative research one mind fertilizes another, and the scientific investigation grows in both depth and breadth. It was the importance of collaboration in research that Claude Bernard was extolling when he wrote: "Art is I; Science is We."

8. Apply for Funding

In this enlightened era of science which is intermittently darkened by the clouds of anti-science and the resultant constraints of research budgets from governments and other agencies it should be encouraging for you, as a potential clinician-scientist, to realize that there *is still* money available to support well-planned, clearly stated, exciting, significant and original research. The peer review system would still seem to be the most appropriate mechanism whereby your grant application may receive the fairest consideration; at the same time the highest possible standards of research may be maintained.

Two of the criteria by which your fellow scientists in the peer review system judge a given proposal are the scientific significance of the project in terms of new knowledge or understanding and also the likelihood of its success.

9. Conduct the Investigation

Through the scientific investigation you set out neither to prove nor to disprove your hypothesis but rather to test its validity with complete objectivity.

As a clinical physician or surgeon your inherent reverence for human life and human comfort will compel you to confine *experimental* investigations to animals and also to accept the principle that any proposed *clinical* investigations in humans must be morally and ethically acceptable to the review mechanism of a university-based "Human Clinical Investigation (or "Experimentation") Committee" which includes clinician-scientists as well as members of other professions. Experimental investigations in animals must also be acceptable in that they must meet established government regulations to protect the comfort of the animals.

10. Collect and Analyze the Data

As you make observations and collect data during the progress of your investigation you should be alert to the possibility that an unexpected finding may have much significance — the phenomenon of *serendipity* (a word coined by Horace Walpole and based on the story of the Three Princes of Serendip who during a long journey never did reach their planned goal but who, unexpectedly and by chance, found many things of even greater interest and significance along the way). Indeed, many important discoveries have been made through serendipity — penicillin, polio vaccine, and cryoprecipitate to mention only three.

A serendipitous observation, of course, should stimulate another cycle of research. But the scientist may fail to appreciate the significance of the unexpected as Churchill pointed out when he wrote "Man occasionally stumbles over the truth but he usually manages to pick himself up and continue on."

Provided that the protocol of your investigation has been well planned it should be possible for you to analyze your data accurately and to determine its statistical significance.

11. Interpret the Data

This phase of the cycle of medical research is one of the most important because you may have collected important data but unless your interpretation of these data is correct you may find yourself off your cycle and into the ditch of delusion.

In the interpretation of the data you must consider all of the data and not just those parts that seem "to fit" your hypothesis because through the latter process you would, in fact, be deluding yourself — and others; you would be making the facts fit the theory rather than, as you should be, making the theory fit the facts. It may have been this type of intellectual dishonesty that George Bernard Shaw was contemplating when he wrote "Beware of false knowledge — it is more dangerous than ignorance."

12. Draw Valid Conclusions

Through the application of sound logic and scientific reasoning you should draw valid conclusions — in so far as that is possible — on the basis of the factual data. This is another difficult phase of the cycle of medical research since the clinician-scientist may be tempted, subconsciously and unwittingly, to draw conclusions that are not justified by the factual data. When more than one interpretation of the data seem reasonable it may be necessary to initiate another cycle of research to clarify the matter.

13. Answer the Original Question

By the time you have reached this phase of the cycle you may well be able to answer the original question. You should not be disturbed if the answer is not that which you expected because, of course, you are seeking the truth rather than proof of a pre-conceived theoretical answer to the original question. The search for truth, however, is never-ending because the more questions you answer the more questions you will raise to take their place. Each of these questions, in turn, will serve as the catalyst for the creation of another research cycle.

14. Present Results at a Meeting

Having completed the investigation it is important for you to present the results at a scientific meeting in order that you may benefit from the resultant discussion — both positive and negative. Indeed, constructive criticism of a given scientific investigation can only help you to improve upon its final presentation. It would be considered unprofessional for you as a medical scientist to share the results of your research with the general public through the lay media — press, radio or television — before these results have been either presented at a major scientific meeting or published in the scientific literature.

15. Publish a Scientific Paper

If your investigation has been worth doing it is worth publishing and you should seek publication in a reputable scientific journal which is critically refereed. Indeed, you have a moral obligation to publish a significant scientific investigation for as Richard Bach has written in his book entitled Jonathan Livingston Seagull, "It is good to be a seeker but sooner or later you have to be a finder, and then it is well to give what you have found, a gift unto the world for whoever will accept it."

16. Apply the New Knowledge

As implied in the adjective "applied", this type of mission-oriented or targeted research frequently leads to new knowledge that can be applied to the unsolved clinical problem that initiated the cycle of medical research. The application may be relevant to an improved understanding of the etiology, pathology, pathogenesis, detection, treatment, or even prevention of the clinical problem under investigation.

Thus the cycle of medical research is complete and you will have progressed from realistic research to clinical reality. It is hoped that you will have come to appreciate that it is better to move in the best circles of research than to walk the straight and narrow path of empiricism.

No matter how successful a scientist may be in solving problems, his or her "spirit of constructive discontent", of which Voltaire wrote, is self-perpetuating since one good idea begets another and one discovery leads to another.

In the final analysis, the success of any given medical research project will depend upon the intelligence and inquisitiveness of the individual scientist whose goal should be not to follow the established path of clinical empiricism but rather, through research, to explore where there is no path and leave a trail that leads into the future! □

Dr. Salter is respected throughout the world as one of the leaders in medical education and as a major contributor to Orthopaedic Surgery. He has been recognised internationally for his fundamental scientific investigations of musculoskeletal disorders and injuries, and he has advanced the orthopaedic care of children through the development of new and imaginative methods of treatment.

A graduate of the University of Toronto, Dr. Salter is a member of numerous medical societies and boards of directors. He is the author of Textbook of Disorders and Injuries of the Musculoskeletal System, *as well as over 100 scientific articles. He has received numerous honours including a Gairdner Award for Medical Science and in 1981 he was honoured by the University of Toronto through appointment as a* University Professor *"for excellence in teaching and research", a title that he shares with only 14 others in the university. He is currently senior orthopaedic surgeon at The Hospital for Sick Children as well as Professor and Head of the Division of Orthopaedic Surgery.*

ORTHOPAEDICS

The Anterior Cruciate Ligament — A Review

J.T. Bertoia 8T4

Only in the past decade has the anatomy and function of the anterior cruciate ligament been clarified. With this has come an understanding of the mechanisms of injury and the sequelae of recurrent instability, intra-articular pathology, and osteoarthritis. While many operative procedures have been described for control of this instability, only the MacIntosh lateral substitution over-the-top (LSOT) procedure will be discussed.

Anatomy

The anterior cruciate ligament (ACL) originates along the posteromedial aspect of the lateral femoral condyle (fig. 1) and inserts at the intercondylar eminence of the tibia posterior to the anterior horn of the medial meniscus with no attachment to the tibial spines (fig. 2). Most authors describe two subdivisions, the narrow anteromedial (AM) and broad posterolateral (PL) bundles,[9,15] while Norwood[17] describes a third subdivision, the intermediate bundle. The condylar origin is an anteriorly concave crescent with the AM bundle originating superior to the PL bundle. The tibial attachment is roughly triangular with the apex directed posteriorly, where the PL bundle inserts. The AM bundle inserts anteromedially while the intermediate bundle inserts anterolaterally. The AM bundle is longer than the PL bundle, with both bundles longer in extension than flexion.

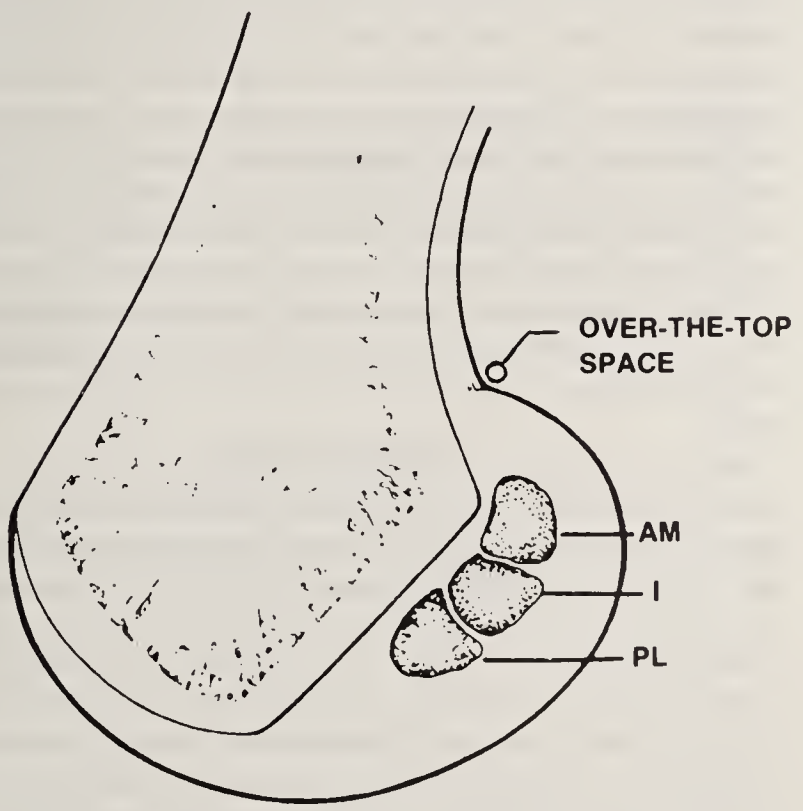


Figure 1: Origin of the anterior cruciate ligament on the posteromedial aspect of the lateral femoral condyle. The 'over-the-top' space is indicated.

Gross examination reveals a multifascicular ligament with the fascicles spiralling from medial to lateral (AM) or running directly from femur to tibia (PL). This spiral nature may account for the lengthening in extension. The ligament is surrounded by a synovial sheath (supplied with blood vessels and nerves [14]) which in some cases delineates the separate bundles [17]. The major blood supply, a branch of the middle geniculate artery, descends on the dorsal surface bifurcating at the tibial spine to form the tibial intercondylar arteries. However, the major nutrient supply is via synovial diffusion. The nerve fibres are of two types. Those that are perivascular are involved in vasomotor control while those that ramify freely through the interfascicular loose connective tissue either transmit impulses of 'slow pain' accompanying ligamentous injury or are involved in proprioception. [14]

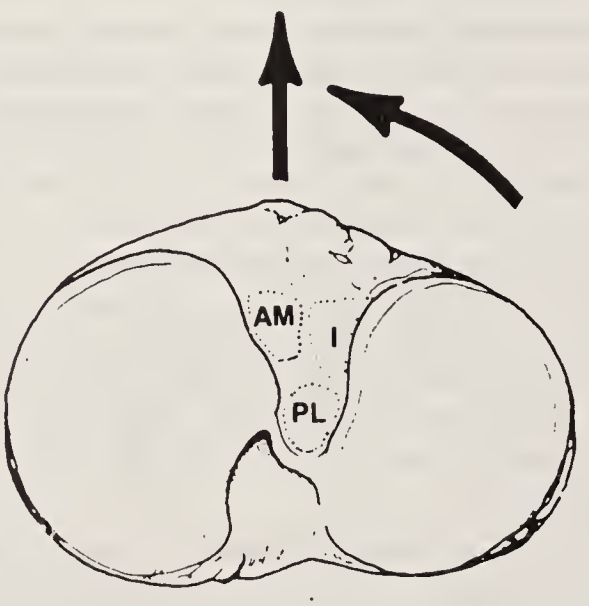


Figure 2: View of the right tibial plateau showing the insertion of the anterior cruciate ligament. The arrows indicate the two directions of displacement of the tibia relative to the femur with anterior cruciate ligament insufficiency — anterior (linear) and antero-lateral (rotational). (modified from Norwood, L.A. and Cross, M.J.: Anterior Cruciate Ligament: functional anatomy of its bundles and rotary instabilities. Am. J. Sports Med. 7:1:23-26, 1979.)

Function

Knee instabilities are described by the movement of the tibia relative to the femur and are classified into three major categories — simple linear, simple rotational, and combined.

There is continuing controversy in the orthopedic literature, a discussion of which is beyond the scope of this paper, with respect to the roles of the medial and lateral ligamentous complexes in the genesis of knee instabity.[9,10,23] The medial ligamentous complex consists of the medial capsular ligament, the medial quadriceps retinaculum, the tibial collateral ligament, and the postero-medial complex, while the lateral complex is composed of the lateral capsular ligament, the lateral quadriceps retinaculum, the fibular collateral ligament, the iliotibial band, the arcuate ligament, and the tendon of popliteus.

The AM bundle of the anterior cruciate is taut at 90° flexion and the PL bundle is taut in full extension. The ACL is the primary check against instability in the following planes of motion:[6,15] (i) anterior dispacement of the tibia in neutral rotation in flexion (AM) and extension (PL), (ii) internal rotation in flexion (both AM and PL) and extension (either AM or PL) and (iii) hyperextension (PL). Secondary restraints are the Iliotibial band and tract, and the medial and lateral collateral and capsular ligaments.[3]

There are three proposed mechanisms of injury: The first involves hyperextension (PL) ± internal rotation (AM)[6]. The second deals with flexion and external rotation with an applied lateral (valgus) force which levers open the medial compartment, resulting in a torn medial collateral ligament with an associated peripheral medial meniscal tear due to its capsular attachment. With continued force, the ACL is stretched over the lateral femoral condyle leading to its rupture.[21] This triple injury was first described in 1950 and has come to be known as O'Donoghue's triad.[19] The third mechanism consists of a posterior force leading to anterior subluxation or discloation of the tibia on the femur.[14]

Presentation

Most commonly, a young athlete presents after a twisting injury or a direct blow to the knee associated with severe pain and inability to continue play, often being unable to walk unaided. The patient frequently describes hearing a 'pop' or feeling a 'snap' at the time of injury. Arnold[1] and Marshall[15] have found that greater than 90% of patients reporting this symptom have a torn anterior cruciate ligament. A traumatic hemarthrosis develops within two hours (as compared to a synovial effusion which takes 12-24 hours to evolve) unless there is an associated capsular tear allowing the blood to extravasate into the surrounding soft tissues.[15] Torn anterior cruciate ligaments account for more than 75% of acute hemarthroses.[15,18]

The patient seeks medical attention, has an X-ray taken (usually read as normal) and is sent home with the diagnosis of a 'sprained knee'. This is followed by a period of recovery with a gradual return to sports. Activity stretches the secondary support structures (vide supra) leading to unpredictable recurrent "giving way", usually precipitated by twisting or pivoting, with associated pain and swelling lasting from two to ten days.

While the complete knee examination should be performed (Table 1), special emphasis is placed on the anterior drawer and pivot shift tests.

The anterior drawer test is performed at 90° of flexion. The foot is stabilized in neutral rotation and the tibia is grasped and pulled directly forward. Anterior displacement is measured in comparison to the contralateral side. Since the AM band is taut in flexion, it must be ruptured for a positive test.[6,15] The PL bundle then becomes the new primary restraint. Performing this test with 30° of internal rotation and 15° of external rotation allows assessment of the lateral and medial complexes respectively.[21] The anteriar drawer test can also be done at 5-10° of flexion, in which case it is known as the Lachman test. This is more specific for ACL insufficiency but is more difficult to perform.

The second important test is the pivot shift or MacIntosh test which is pathognomonic for ACL insufficiency.[7] The leg is held in extension with the foot in internal rotation. A valgus (lateral) force is applied as the knee is flexed. As flexion begins, the posterior capsule and posterior cruciate ligaments relax allowing anterolateral subluxation of the tibia of the femur. With further flexion, the posterolateral corner of the tibia impinges on the lateral femoral condyle. This levers the anterior aspect of the joint open, tensing the lateral and peripatellar structures in addition to the medial structures made taut due to the valgus force. At 30-40° of flexion, there is a sudden reduction of the tibia. This jumping sensation characterizes a positive test and will be identified by the patient as being identical to the sensation felt when the knee "gives way".

In the acute situation, these tests may be negative due to patient guarding and hemarthrosis and later, due to tautness of the secondary restraints. Properly applied, it is possible to differentiate complete from partial tears and, in the latter case, to determine which bundle is ruptured. For example, a positive anterior drawer test associated with a negative pivot shift test would suggest a tear of the antero-medial bundle alone.

Should they be repaired?

Aside from the immediate effects of instability, there is evidence that chronic instability will lead to early degenerative changes. A ten year follow-up of 50 patients with unrepaired ACL insufficiency found that while 72% of the patients had returned to sports, 53% felt their activities were in some way restricted and 75% demonstrated early to late degenerative osteoarthritic changes on radiographic examination.[16] Richards et al[20] analyzed the relationship between the location and type of intra-articular pathology and the duration of ACL insufficiency and demonstrated that the incidence of intra-articular pathology increased linearly with time. These studies indicate that recurrent "giving way" increases the degree of intra-articular pathology ultimately leading to osteoarthritis, and that damage is not solely due to the initial traumatic event.

While Hey Groves,[8] in the early part of this century, was advocating operative repair for late instability, most surgeons felt the ACL was not, in and of itself, of great importance and few attempts were made to repair it. In 1950, O'Donoghue[19] advocated primary repair of the ligament in the acute setting. Through the 1960's, a variety of procedures were developed to correct the late instability.[4,7] However, it was not until 1968 that the concept of ACL insufficiency causing rotational instability, as opposed to a strictly anterior instability, was formally introduced.[21] This was, however, incorrectly described as being an anteromedial rotational instability. In 1972, Dr. MacIntosh, of the Toronto General Hospital, suggested the currently accepted view that the rotational instability was in fact anterolateral and described the pivot shift test[7] which is pathognomonic for this instability. A plethora of operative

procedures have been described utilizing the semitendinosus,[4] gracilis,[22] and patellar tendons,[13] the iliotibial band,[5,8,11,12] other structures about the knee to correct this problem.

In the acute setting, a primary repair is often attempted, supplemented with a patellar tendon or iliotibial band graft.

For late reconstruction, the operative procedure commonly performed in Toronto is the lateral substituion over-the-top (LSOT) developed by Dr. MacIntosh. A 4 cm. by 30 cm. strip of fascia lata is detached proximally and freed down to its insertion at Gerdy's tubercle. This is then passed proximally medial (deep) to the lateral collateral ligament, anterior to the origin of the lateral gastrocnemius muscle and over-the-top of the lateral femoral condyle. The graft is passed along the line of the absent ACL through a drill hole at the former insertion of the ACL to appear medial to the tibial tubercle. The graft is then passed posterior to the patellar tendon back to its origin at Gerdy's tubercle. Thus, this procedure combines both an extra-articular and an intra-articular repair. The patient is able to return to full activities in about nine months to a year.

In a recent study by the author,[2] thirty-four patients were assessed an average of 35.3 months post-operatively. Thirty-three patients (97%) returned to recreational or competitive sports, with only two (6%) reporting episodes of "giving away". On examination, thirty-one (91%) patients had a negative pivot shift test, while 88% had a positive anterior drawer test. These results compare favourably with those reported for other procedures.

Conclusion

To quote Don O'Donoghue, "The time to diagnose an injury to the knee is at the time of injury. . .often examination is not made until weeks later, when manifest instability and disability demand something be done. . .reconstruction instead of repair must be undertaken with a resulting loss of time, increase in extent of surgery and impairment of chances for complete success."[19]

It is therefore incumbent upon the family and emergency room physician to be thoroughly versed in the knee examination. With the increased interest and activity in sports in the general population, it seems reasonable to expect an increase in incidence and a change in the demographics of this injury. With early recognition and treatment, it is felt that the late sequela of recurrent instability, namely osteoarthritis, may be avoided. □

Acknowledgements

The author would like to thank Dr. A.E. Gross, Mount Sinai Hospital, Toronto, and Dr. W. Brown, Dept. of Anatomy, University of Toronto for their help in the preparation of the manuscript.

Table I — The Knee Examination

I. Inspection — swelling (effusion vs. hemarthrosis)
— contusions

II. Palpation: 1. General
— temperature
— effusion
— range of motion

Compartments
A. Patello-femoral
— patellar size and mobility
— tenderness
— crepitus
— Fairbank's test
— quadriceps inhibition test
B. Medial and Lateral
— joint line tenderness
— crepitations
— collateral ligament tenderness
— collateral ligament stability in extension and flexion (20 - 30°)

3. Cruciate ligaments
A. Anterior
— anterior drawer test
— Lachman test
— pivot shift test
B. Posterior
— posterior sag

4. Menisci
— McMurray test

5. Popliteal space
— tenderness
— swelling
— pulse

References

1. Arnold, J.A., Coker, T.P., Heaton, L.M., park, J.P., Harris, W.D.: Natural History of Anterior Cruciate tears. *Am. J. Sports Med.* 7:6:305, 1979.
2. Bertoia, J.T., Urovitz, E., Gross, A.E., Richards, R.: Anterior Cruciate Reconstruction — The MacIntosh Lateral Substitution Over-the-top (LSOT) *Repair* in preparation.
3. Butler, D.L., Noyes, F.R., Grood, E.S.: *Ligamentous Restraints to Anterior - Posterior Drawer in the human knee.* JBJS: 62-A:687, 1980.
4. Cho, K.O.: *Reconstruction of the anterior cruciate ligament by semitendinosus tenodesis.* JBJS: 57-A:608, 1975.
5. Ellison, A.E.: *Distal iliotibial band transfer for antero-lateral rotatory instability of the knee.* JBJS: 61-A:330, 1979.
6. Furman, W., Marshall, J.L., Girgis, F.G.: *The anterior cruciate ligament.* JBJS: 58-A:179, 1976.
7. Galway, R.B., Beaupre, A., MacIntosh, D.L.: *Pivot shift:* A clinical sign of symptomatic anterior cruciate insufficiency. JBJS: 54-B:763, 1972.
8. Hey Groves, E.W.: *The crucial ligaments of the knee joint:* Their function, rupture, and operative treatment of the same. Br. J. Surg. 7:505, 1920.
9. Hughston, J.C., Andrews, J.R., Cross, M.J., Moschi, A.: *Classification of Knee Ligament Instabilities.* Part I: The medial compartment and cruciate ligaments. JBJS:58-A:159, 1076.
10. Hughston, J.C., Andrews, J.R., Cross, Moschi, A.: *Classification of Knee Ligament Instabilities.* Part II: The Lateral Compartment. JBJS:58-A:173, 1976.
11. Install, J., Joseph, D.M., Aglietti, P., Campbell, R.D.: Bone-block Iliotibial Band transfer for *Anterior Cruciate insufficiency.* JBJS:63-A:560, 1981.
12. Ireland, J., Trickey, E.L.: MacIntosh tenodesis for *antero-lateral instability of the knee.* JBJS:62-B:340, 1980.

13. Jones, K.G.: *Reconstruction of the Anterior Cruciate Ligament:* A technique using the central one-third of the patellar ligament. JBJS:45-A:925, 1963.

14. Kennedy, J.C., Weinberg, H.W., Wilson, A.S.: *The anatomy and function of the anterior cruciate ligament.* JBJS:56-A:223, 1974.

15. Marshall, J.L., Rubin, R.M.,: *Knee ligament injuries* — A diagnostic and therapeutic approach. Ortho. Clin. N.A.8:3:641, 1977.

16. McDaniel, W.J., Dameron, T.B.: *Untreated ruptures of the anterior cruciate ligament.* JBJS:62-A:696, 1980.

17. Norwood, L.A., Cross, M.J.: *Anterior Cruciate Ligament:* functional anatomy of its bundles in rotatory instabilities. Am J. Sports Med. 7:1:23, 1979.

18. Noyes, F.R., Bassett, R.W., Groad, E.S., Butler, D.L.: *Arthroscopy in Acute Traumatic hemarthrosis of the knee.* JBJS:62-A:687, 1980.

19. O'Donoghue, D.H.: *Surgical treatment of fresh injuries to the major ligaments of the knee.* JBJS:32-A:721, 1950.

20. Richards, R., Esses, S., Langer, F., Gross, A.E.: *The intra-articular pathology associated with anterior cruciate insufficiency.* in Proceedings — Dewar Club — 1980.

21. Slocum, D.B., Larson, R.L.: *Rotatory instability of the knee.* JBJS:50-A:211, 1968.

22. Thompson, S.K., Calver, R., Mark, C.J.E.: Anterior cruciate ligament repair for rotatory instability: *The Lindemann Dynamic Muscle Transfer procedure.* JBJS:60-A:917, 1978.

23. Warren, L.F., Marshall, J.L.: *The supporting structures and layers in the medial side of the knee.* JBJS:61-A:56, 1979.

ONCOLOGY

Clinical and Pathological Aspects of Nasopharyngeal Carcinoma

Andie Lam 8T4

This paper is a review of some of the features of nasopharyngeal carcinoma, a squamous cell cancer with variable lymphocytic infiltration which tends to show a racial predisposition in the Cantonese Chinese from southeast China. As well, this tumour is one human malignancy which seems to implicate a virus in the etiology of disease, the Epstein-Barr virus. The proximity of the nasopharynx to several cranial nerves and other important structures may result in a diversity of florid signs and symptoms in the patient. Finally, this is one cancer in which patient management relies almost exclusively in radiation therapy.

Introduction

Malignant neoplasms of the nasopharynx occur at a higher frequency than benign tumors, and nasopharyngeal carcinoma (NPC) is among the most frequent cancers affecting the Cantonese people of the Kwantung province in southeast China. Peculiarly, this type of tumour is relatively rare in white and black racial groups, as well as in Chinese of a different regional extraction.

Previously, this has been a lethal disease in that there is a predisposition for early invasion and metastasis into surrounding structures (e.g., cervical lymph nodes), despite the rather rigid confines of the region. However, advances in radiation therapy over the past few decades have significantly improved the patient's prognosis, to the extent that radiation plays the major role in patient management today, while surgery and chemotherapy occupy a comparatively lesser role.

NPC is unusual in that the presenting symptoms are not directly referable to the nasopharynx itself, but rather to its anatomical relationships. Hence, an understanding of the anatomy of the region is essential in order to rationalize patient's otitic and nasal complaints (e.g., hearing loss or epistaxis). A patient presenting with such symptomatology should draw the physician's suspicions to the nasopharynx as a primary source of the problem.

In this brief paper an attempt will be made to delineate some of the features of this peculiar tumour such as its etiology, epidemiology, pathology, and clinical presentation. But first a terse depiction of some relevant anatomy is in order.

Anatomy of the Nasopharynx

The nasopharynx is a cuboidal chamber posterior to the nasal cavities with which it freely communicates. The roof of the chamber consists of the sphenoid and basiocciput bones of the skull which merge with the posterior wall formed by the arch of the atlas and the superior portion of the body of the second cervical vertebra (see figure 1).

The lateral walls of the nasopharynx are clinically the most significant landmarks in regards to NPC. The two Eustachian tubes have their openings into the pharynx here. The torus tuberius is the internal extension of the cartilaginous part of the tube posteriorly into the pharynx. Behind the Eustachian orifice, and between it and the posterior wall, is the lateral

pharyngeal recess or fossa of Rosenmüller, an important clinical entity. The recess expands freely into the posterior nasal choanae anteriorly, and the oropharynx inferiorly via the pharyngeal isthmus. Both the fossae and the posterior wall embody patches of lymphoid tissue in their mucosa. These patches are a likely source of lymphocytes found in some NPCs. Lastly, the floor of the nasopharynx consists of the superior surface of the soft palate.

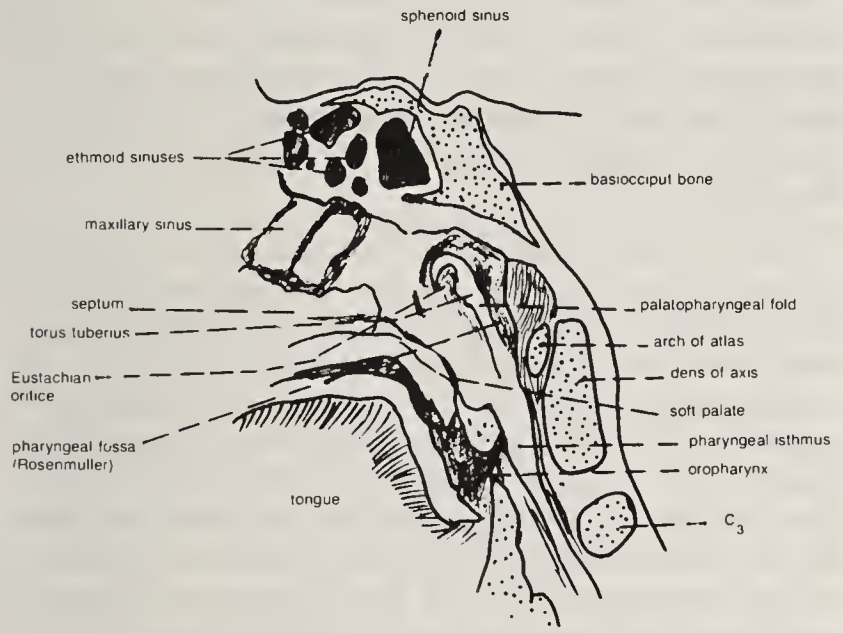


Fig. 1. Midsagittal section of the nasopharynx. (Adapted from Choa, G., *Cancer of the Nasopharynx*. In "Cancer of the Head and Neck", Suen, J.Y. and Myers, E.N., Editors. Churchill Livingston Inc., New York, 1981. page 373.)

An extensive lymphatic capillary plexus is formed throughout the region. Although efferent lymph vessels here generally drain into the ipsilateral nodes, connections do exist with contralateral nodes. Therefore, a primary malignant growth on one side of the nasopharynx may disseminate to the same side of the neck as well as to the opposite side. The principal drainage basin is the lateral retropharyngeal nodes which are situated high up in the neck near the base of the skull, anterior to the body of the atlas (see figure 2). The nodes are located in close proximity to the internal carotid artery, internal jugular vein, the last four cranial nerves, and the superior sympathetic ganglion. This has clinical significance as described later. The deepness of the retropharyngeal nodes in the neck makes their palpation impossible. They drain into the deep cervical nodes of the posterior triangle and the jugulodigastric nodes. The latter also receive branches directly from the nasopharynx.

Etiology and Epidemiology

Although the nasopharynx is not a common site of pharyngeal cancer, NPC is one of the most frequent cancers found in Cantonese Chinese of the Kwantung Province, Hong Kong, Singapore, and Macao[13,17] (see figure 3). In particular, NPC accounts for 18% of all cancers and 13% of all deaths from cancer in Hong Kong.[3,15] The figures are striking when they are compared to 0.25% for the incidence of NPC worldwide and 0.5% for the death rate in most other countries.[1,14] The incidence of this cancer in northern and eastern European peoples is very low, but rises with certain Mediterranean societies, for example, the Italians and Greeks.[20] NPC accounts for less than 1% of all cancers in the United States.[19]

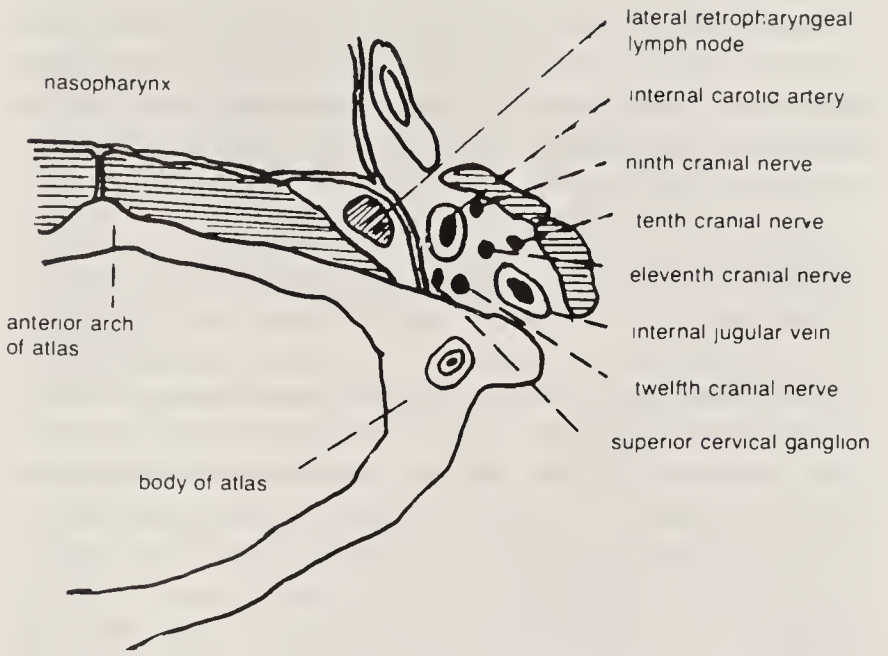


Fig. 2. Transverse section through the nasopharynx showing its relationship to the parapharyngeal space and its contents. (Adapted from Ranger, D., *Tumours of the Pharynx*. In "Scott-Brown's Diseases of the Ear, Nose and throat, Volume IV: The Pharynx and Larynx", 4th ED., Ballantyne, J., and Groves, J., Editors. Butterworth and Co. (Publishers) Ltd., London, England, 1979. page 172.)

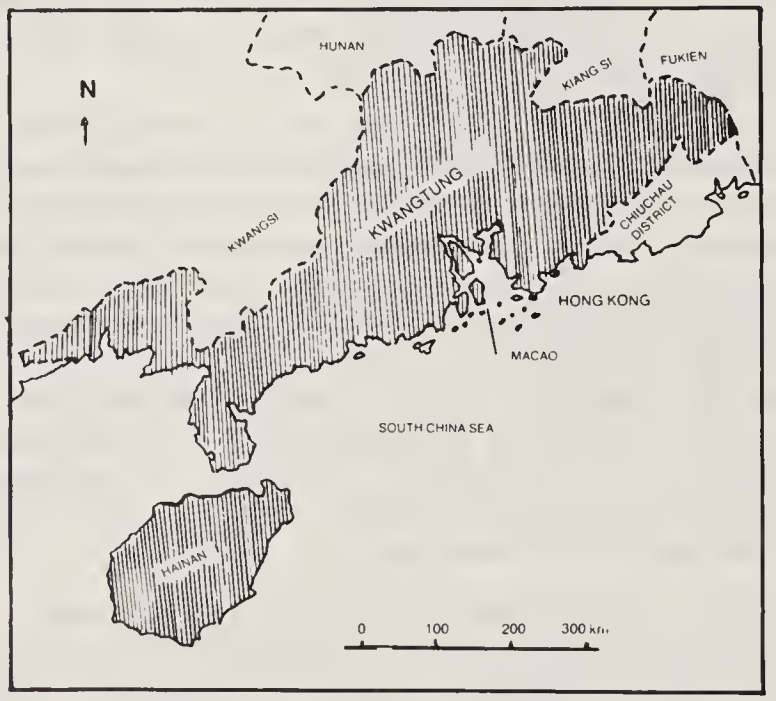


Fig. 3. Map of the Kwantung Province, China. (Adapted from Choa, G., *Cancer of the Nasopharynx*. In "Cancer of the Head and Neck", Suen, J.Y. and Myers, E.N., Editors. Churchill Livingston Inc., New York, 1981. page 373.)

Sturton, Wen and Sturton report that this high incidence of NPC in unique to the Kwantung Province, and it is not seen in other provinces of China, strongly suggesting a subracial predisposition for the disease. [15] This point is reinforced by Buell's study of Californian Chinese immigrants (chiefly of Kwantung origin) who showed a 30-40 times greater mortality rate from NPC as compared to Californian Caucasians. [2] In effect, their risk was identical to that of the mainland Cantonese Chinese. Moreover, their Chinese children born in the U.S. demonstrated a 20 times differential mortality relative

to their American counterparts. Because of this transference of risk to the second generation, Buell presupposes a genetic susceptibility in the Chinese as part of the etiology of the disease.

Numerous other variables which may play a role in the causation of NPC have been postulated, but the relative implications of each are so far not determinable. Perhaps the etiology of this tumour is most likely associated with a multifactorial process.

There is an association between Epstein-Barr virus (EBV) and NPC, but the precise role this virus plays in the etiology of the disease is still far from certain. From serological, immunofluorescence, and electron microscopic investigations, EBV has been shown to be implicated in the causation of certain neoplasms, namely NPC and Burkitt's lymphoma.[4,5,10] Also, injection of EBV or EBV-infected cells into animals can result in cellular transformation and ultimately malignancy. Precipitating antibodies to EBV have been discovered in the sera of patients with NPC or Burkitt's lymphoma.[6] Work by Uhlmann *et al* established that consistently high titers of Epstein-Barr viral capsid antigen (VCA) are found in patients with NPC, and the corresponding antibodies are seen in patients with NPC of the anaplastic or "lymphoepithelial" varieties.[18] The viral genomes are carried by the cancer cells themselves and not by normal host cells. Interestingly, antibody titer to VCA increases with severity of disease and levels fall in patients successfully treated and with no residual tumour. As well, NPC patients may have high serologic reactivity against EBV early antigen.

In spite of the amount of circumstantial evidence, Batsakis (1979) still raises legitimate questions over the specificity of association between NPC and EBV. He notes correctly that a majority of adults in all countries are infected by EBV, and after a primary infection, the virus most likely becomes a permanent inhabitant of the nasopharynx in these patients and induces the formation of host antibodies. Hence EBV may be more of a "spectator" than an "actor" in the causation of cancer. Nevertheless, it is noteworthy that the three diseases caused by or associated with EBV — infectious mononucleosis, Burkitt's lymphoma, and NPC — all chiefly involve the head and neck areas.

Sturton, Wen and Sturton speculate that incense smoke and cooking fumes employed by the Chinese in worship may play some role in the causation of cancer.[15] Ho's studies tend to refute this theory, since he points out that Chinese boat people in Hong Kong harbour, who could easily avoid the fumes and smoke of cooking and worship, still have a significantly higher incidence of NPC than the rest of Hong Kong's land dwellers.[7,8] Secondly, Buddhist monks, who are constantly exposed to incense smoke, very seldom develop this type of malignancy. Ho believes the higher incidence of NPC found in the boat people may be attributed to the regular feeding of their children with salted fish. A potent carcinogen, nitrosamine, can be generated in the food during the salting process. As well, the low intake of Vitamin C by the boat inhabitants may be important since Vitamin C is a blocker of amine nitrosification to nitrosamines in the GI tract.

Two other factors postulated in the etiology and which will not be elaborated are: 1) chronic non-allergic vasomotor rhinitis which is common in Hong Kong Chinese has been shown to induce squamous metaplasia and eventually squamous carcinoma *in situ*; and 2) a difference in the configuration of the southern Chinese skull compared to the northern Chinese's does exist, and this dissimilarity could conceivably facilitate the deposit of nasal discharge and inhaled carcinogens.

Pathology and Classification of NPC

Over the years, there has been a lack of uniform pathological classifications of nasopharyngeal neoplasms. Consequently, there is some danger in transferring tumour frequency and survival statistics from one hospital to another as criteria for diagnosis may not be identical in the two institutions.

There is little agreement on classification on the basis of histopathology. However, it is generally concurred that NPC falls into the squamous cell carcinoma type (SCC), of which there are two subdivisions: keratinizing SCC and nonkeratinizing SCC. It is relatively straightforward to identify SCC of the keratinizing type microscopically: one searches for keratin production, intercellular bridges, increased nucleus to cytoplasm ratio and so on. However, SCC of the nonkeratinizing type usually does not manifest any of the above telltale features, and consequently numerous other names have been attached onto it such as transitional cell carcinoma, anaplastic carcinoma, lymphoepithelioma, to name only a few.

The term lymphoepithelioma has been and still is utilized widely by clinicians and deserves some comment. It describes a nonkeratinizing, nonglandular, undifferentiated SCC which has numerous host lymphocytes scattered amongst the tumour cells, hence the designation "lymphoepithelioma". Although no evidence of squamous differentiation is observed by light microscopy, electron microscopy clearly indicates that it is present, due to the finding of keratin fibrils and desmosomes in the lymphoepithelioma cells.[16] The prominent lymphocytic component in this tumour is believed to be purely incidental and has no role in the causation of the lesion, and lymphocytes may or may not be present in the metastases of this tumour. As already mentioned, patches of lymphoid tissue are found regularly beneath the nasopharyngeal mucosa.

In summary then, malignant neoplasms of the nasopharynx are mostly carcinomas, classified into keratinizing and nonkeratinizing SCC. The latter entity predominates, but even keratinizing SCC tends to be poorly differentiated. The cancer cells themselves may be spindle cells or clear cells or a combination of both. Other cancers of the nasopharynx occur less commonly and include lymphoma, adenocarcinoma, adenoid cystic ccarcinoma, melanoma, plasmacytoma, and chordoma.

Clinical Features

NPC tends to occur at a younger age in patients than do most other solid tumours. The peak incidence is in the 40-44 year old group in males and 60-64 year old group in females. The male to female ratio is two or three to one worldwide. The commonest sites of cancer are the lateral walls or fossae of Rosenmuller (43%) followed by the roof (34%). The floor and dorsal surface of the soft palate comprise less than 1%.

Direct infiltration of tumour into surrounding structures follows anatomical pathways. Anterior extension leads to the nasal fossae: the septum (medical wall), the hard palate (floor) or the medial pterygoid plate (lateral wall) may be involved. Inferior dissemination of cancer inevitably involves the oropharynx via the pharyngeal isthmus.

Clinically the most significant route of infiltration is associated with the postero-lateral nasopharyngeal wall, where spread of tumour occurs via the sinus of Morgagni into the parapharyngeal space (see figure 2). Here lie the last four cranial nerves, the superior cervical ganglion, the internal carotid artery, and internal jugular vein. All of these exit from or enter the cranial cavity through foramina related to the postero-lateral wall. Any of the above vessels, nerves, or ganglia may be attacked by cancer; the nerves are particularly susceptible.

The foramen lacerum constitutes a portion of the roof of the fossa of Rosenmüller, as does the floor of the canal for the internal carotid artery. Hence, these two passageways provide a course for the intracranial propagation of tumour, especially if it is a tumour originating in the Rosenmüller fossa or roof of the nasopharynx. In this manner, either the fifth or sixth cranial nerves or both may be compromised. The Eustachian tube, which is situated in the lateral wall, is likewise susceptible to direct infiltration. Invasion of the orbit occurs indirectly, either intracranially via the cavernous sinus or extracranially via the nasal fossa. Proptosis results; yet blindness due to optic nerve embarassment rarely ensues.

NPC frequently metastasizes to the neck nodes due to the rich lymphatic supply in this region, and some 70-90% of patients have palpable nodes when first seen. Nodal involvement is widespread and often bilateral (40%) because of lymphatic crossover. The deep upper jugular chain located at the apex of the posterior triangle is most frequently affected, and it is claimed that a deep palpable node beneath the upper posterior aspect of the sternomastoid muscle is virtually pathognomonic of a nasopharyngeal tumour. Other nodes which are often involved include the middle and lower deep cervical nodes, the accessory and supraclavicular nodes, and the submaxillary and sublingual nodes. An inverse relationship exists between the degree of differentiation of a tumour and its likelihood to metastasize to the neck nodes. Consequently, more than 90% of patients suffering from lymphoepitheliomas or undifferentiated squamous cell carcinomas will have signs of positive nodes. In late disease, there may be tumor propagation to sites as distal as the inguinal nodes and cases have been reported of generalized lymphadenopathy as a result of extensive tumour metastasis.

Distant metastases occur in about 20% of patients. The skeleton is the most frequent site, followed by lungs and liver. Although central nervous tissue infiltration by tumour is not known to occur (even when the skull base itself is invaded), the meninges can be seeded by cancer cells, giving rise to signs and symptoms of frank meningitis. [20] In fact, a patient may initially present in this manner. Survival is very much shortened when distant metastases emerge. One study quotes a median survival of less than four months and a fatality rate of greater than 90% within the first year. [9]

A patient with NPC of any differentiation state rarely presents with symptoms directly referable to the nasopharynx itself. The earliest and some of the most common manifestations are related to the obstruction of the nasal airway and the Eustachian tube. Conductive deafness, uni- or bilateral, due to middle ear effusion, is often the first reported complaint. This may be caused by nasopharyngeal inflammation, infiltration of the torus by growing cancer cells, or by direct assault of the tubal opening. Yet infiltration into the middle ear cavity is seldom seen. Other otitic complaints are tinnitus and a sensation of stuffiness. Nasal obstruction is a consequence of blockage of the choanae or actual tumour spread into the nasal cavity.

Profuse epistaxis is rarely observed, but a NPC should be suspected if it is presented, particularly if most of the blood drips down into the pharynx in the upright position.

Later, neurological symptoms develop due to tumour extension into the cranial nerves. Several structures from a portion of the roof of the Rosenmüller fossa, the primary site of cancer growth. These are the foramen lacerum and part of the petrous temporal bone and its adjacent cavernous sinus which houses the trunks of cranial nerves III to VI and the internal carotid artery. The trigeminal nerve (Cr. V) is the most frequent and earliest nerve affected. The maxillary (V2) and mandibular (V3) divisions are most often involved, giving rise to temporal headaches, tactile anesthesia and facial pain. Loss of the corneal reflex is not an uncommon complication of Cr. V damage. The abducens nerve (Cr. VI) is the second most frequent nerve of involvement: medial strabismus and diplopia ensue. If Cr. IX to XII are impaired by tumour, the patient may complain of dysphonia, dysphagia, and shoulder weakness. Indeed, virtually any cranial nerve except Cr. II can be injured by the invading tumour mass.

With respect to SCC of the nasopharynx, and especially lymphoepithelioma, cervical node enlargement is often the first sign, even when the primary growth is clinically undetectable and not giving rise to other symptoms. Thus, if a patient presents with neck swelling suggestive of enlarged cervical nodes, no biopsy should be undertaken until after a thorough examination of the structures draining into these nodes, including the nasopharynx.

Besides a complete nasopharyngeal examination using a scope and mirror, radiology and tomography are also very beneficial to help make or confirm a diagnosis. A film of the base of the skull as well as a lateral soft tissue film should be made. Lederman reports that 20% of patients show destruction of the base of the skull as evidenced by radiographs. [11]

The definitive procedure for diagnosis is biopsy, especially if both clinical and roentgenographic studies prove negative. A biopsy should be taken of both the Rosenmüller fossae and the posterior wall and roof. If there is a high index of suspicion and the first biopsy proves to be negative, repeated biopsies are justified. Biopsy of enlarged neck nodes is often unnecessary since it does not always indicate the primary site of cancer; this operation should be attempted only after an entire study of the nasopharynx and other areas has yielded little information.

Treatment and Prognosis

Management of a patient with NPC should commence with a histological evaluation of the type of tumour and a thorough assessment of the extent of disease. It is clear that the stage of the disease dictates the ultimate prognosis, namely life expectancy and quality of life for the patient.

The anatomical location of the nasopharynx and its proximity to the base of the skull and several cranial nerves make surgery (especially block dissection) impractical for a patient with NPC. This is one cancer in which radiotherapy plays a supreme role in treatment, to the extent that a patient's prognosis essentially hinges on the relative success or failure of megavoltage irradiation. Radiotherapy should be directed to the entire nasopharynx, the retropharyngeal lymph nodes, and all of the lymph nodes in both sides of the neck whether they are palpable or not. If there is tumour infilitration into the skull base and surrounding structures, then these should be included in the radiation fields. The principal reason for failure of radiotherapy is because most patients present with advanced disease when first seen. At least 50% have cervical node metastases, and some are complicated further by spread of tumour into the skull base. This latter development poses a limit to the dose of radiation which can be administered without inducing serious neurological side-effects.

What roles do surgery or chemotherapy play? A small fraction of patients presenting with limited, recurrent NPC following a full course of radiation may profit from local surgical resection, provided there are no distant metastases. Radical neck dissection for control of cervical nodal metastases is advocated by some and condemned by others. Dissection is very difficult especially if the carotid sheath or the deep retropharyngeal nodes are affected. Chemotherapy has been applied for patients with recurrent or residual disease after a full course of radiotherapy. The standard pharmacotherapeutic agents such as methotrexate, cyclophosphamide, and bleomycin, whether administered alone or in combination, have in general proved disappointing and have not improved patient survival. A reason for the poor response may be the low blood supply to the nasopharynx. However, studies are currently being conducted to determine whether pre-radiation dispensation of combination chemotherapeutic agents (in one or two courses) can significantly ameliorate patient survival.[20]

In regards to staging, the International Union against Cancer (UICC) (1962, 1974) recommends the TNM system of staging cancer development, according to the dimensions of the primary *tumour*, the magnitude of regional lymph *node* involvement, and the presence or absence of tumour *metastasis*(see table 1). More than 50% of patients presenting at T_1 survive five years. It can be appreciated that the extent of nodal involvement or size of primary disease can lower survival rates dramatically (table 2). For example, notice that there is no survival at five years with stage N_3 regardless of the size of the primary lesion. Although data for T_4 are not included in table 2, several researchers publish a survival rate of only 16% after five years in their series.[12] Interestingly, survival rates are better in females, in younger patients, and in patients with the more undifferentiated histological cell types (these are more radiosensitive).

Table 2 denotes an overall survival rate after five years (taking all varieties of carcinoma into consideration) of less than 40%. This is rather optimistic, compared to the series released by other investigators — (Ho (1970): 25%, Godtfredsen (1944): 22%, and Schnohr (1970): 22%).

Nasopharyngeal carcinoma has been and continues to be a dreaded disease in which modern therapeutic techniques still are not able to drastically improve patient survival although quality of life may be augmented. □

Table I: Clinical Staging of Carcinoma of the Nasopharynx*

Tumor Site

T1s Carcinoma *in situ*
T1 Tumor confined to one site of nasopharynx, or no visible biopsy (biopsy positive)
T2 Tumor involving two sites (both posterosuperior and lateral walls)
T3 Extension of tumor into oropharynx or nasal cavity
T4 Invasion of skull or cranial nerves or both

Lymph Nodes

N0 No clinically positive nodes
N1 Single clinically positive and homolateral lymph node; less than 3 cm.
N2 As above; 3-6 cm.' or multiple clinically positive nodes; none greater than 6 cm. in diameter
2A. Single, 3-6 cm.
2B. Multiple, all less than 6 cm.
N3 Massive homolateral node(s), bilateral nodes, or contralateral node(s)
3A. Clinically positive homolateral node(s), one greater than 6 cm.
3B. Bilateral clinically positive nodes (stage both sides of neck separately)

* From Batsakis, J.G., *Tumors of the Head and Neck-Clinical and Pathological Considerations*, 2nd Ed. William and Wilkins Co., Baltimore, 1979, page 197.

Table 2: Five Year Survival (Related stage of disease).*

Primary	N0	N1	N2	N3	Total
T_1	69%	58%	11%	0%	54%
T_2	56%	23%	11%	0%	27%
T_3	36%	18%	25%	0%	26%
Total	54%	38%	—	0%	39%

* From Rubin, P., Editor, *Clinical Oncology for Medical Students and Physicians: A Multidisciplinary Approach*, 5th Edition. American Cancer Society, 1978, page 172.

Acknowledgements

The author is much indebted to Dr. Martin Blackstein of the Mount Sinai Hospital, Toronto, who in spite of his very busy schedule, found the time to provide support and editiorial assistance in the writing of this paper.

Dedication

This paper is dedicated to the memory of my father whose life was taken by nasopharyngeal carcinoma.

Bibliography

Batsakis, J.G. *Tumors of the Head and Neck—Clinical and Pathological Considerations,* 2nd. ed. (Baltimore: William and Wilkins, 1979).

Choa, G. *Cancer of the Nasopharynx.* In "Cancer of the Head and Neck", Suen J.Y. and Myers, E.N., Editors. (New York: Churchill Livingstone Inc., 1981).

MacComb, W.S. and Fletcher, G.H. *Cancer of the Head and Neck.* (Baltimore: William and Wilkins, 1967).

Ranger, D. *Tumours of the Pharynx.* In "Scott-Brown's Diseases of the Ear Nose and Throat, Vol. IV: The Pharunx and Larynx", 4th Ed., Ballantyne, J. and Groves, J., Editors. (London: Butterworth and Co. Ltd., 1979).

Rubin, P., Editor. *Clinical Oncology for Medical Students and Physicians: A Multidisciplinary Approach,* 5th Ed. American Cancer Society, 1978.

Management Guidelines for Head and Neck Cancer, Section 7. U.S. Dept. of Heath, Education and Welfare, Public Health Service, National Institute of Heath, 1979.

References

1. Bailor, J.C. III: Nasopharyngeal Cancer in White Populations — A Worldwide Survey. *U.I.C.C. (Union Int. Cancer) Monogr. Ser.* 1:18, 1967.
2. Buell, P.: Nasopharyngeal Cancer in Chinese in California. *Br. J. Cancer* 19: 459, 1965.
3. Digby, K.H., Fook, W.L. and Che, Y.T.: Nasopharyngeal Malignancy. *Br. T. Surgery* 28: 517, 1941.
4. Henderson, B.E., Lonie, E.W., Jing, T.S. and Alena, B.: EBV and Nasopharyngeal Carcinoma: Is there an Etiologic Relationship? *J. Natl. Cancer Inst.* 59: 1933, 1977.
5. Henle, W. and Henle, G.: Evidence for an Etiologic Relation of the EBV to Human Malignancies. *Laryngoscope* 87: 467, 1977.
6. Henle, W., Henle, G., Ho, H-C., Cachin, Y., Clifford, P., De Schryver, A., De-The, G., Diehl, V. and Klein, G: Elevated Titers of EBV in Nasopharyngeal Carcinoma, other Head and Neck Neoplasms and Control Groups. *Journal of the National Cancer Institute* 44: 225-231, 1970.
7. Ho, H.C.: An epidemiologic and Clinical Study of Nasopharyngeal Carcinoma. *Int. J. Radiation, Oncology, Biology, Physics* 4: 181, 1978.
8. Ho, H.C.: Nasopharygeal Carcinoma in Hong Kong. In "Cancer of the Nasopharynx", Muir, C.S. and Shanmugaratnam, K., Editors. P.J. Schmidt Publishers, Copenhangen, 1967.
9. Khor, T.H., Tan, B.C., Chua, E.J. and Chia, K.B.: Distant Metastases in Nasopharyngeal Carcinoma. *Clinical Radiology* 29: 27, 1978.
10. Klein, G.: The EBV and Neoplasia. *NEJM* 293: 1353, 1975.
11. Lederman, M.: Malignant Tumour of the Nasopharynx. In "Cancer of the Head and Neck—Proceedings of an International Symposium, Montreux, Switzerland, April 2-4, 1975", Chambers, R.G. *et al,* Editors. Exerpta Medica Publisher, Amsterdam, Netherlands, 1975. pages 131-139.
12. Little, J.B., Schultz, M.D. and Wang, C.C.: Radiation Therapy for Cancer of the Nasopharynx. *Arch. Otolaryngol.* 77: 621, 1963.
13. Martin, H. and Quan, S.: Racial Incidence (Chinese) Of Nasopharyngeal Malignancy. *Ann. Otol., Rhinol.* and *Laryngol* 60: 168, 1951.
14. Omerod, F.C.: Malignant Diseases of the Nasopharynx. *J. Laryngol.* and *Otology* 65: 778, 1951.
15. Sturton, S.D., Wen, H.L. and Sturton, O.G.: Etiology of Cancer of the Nasopharynx. *Cancer* 19: 1666-9, 1966.
16. Svoboda, D.J., Kirchner, F.R. and Shanmugaratnam K.: The Fine Structure of Nasopharyngeal Carcinomas. In "Cancer of the Nasopharynx", Muir, C.S. and Shanmugaratnam, Editors. Munksgaard, Copenhagen, 1967. page 163.
17. Teoh, T.B.: Epidermoid Carcinoma of Nasopharynx Among Chinese: Study of 31 Necropsies. *J. Path. Bact* 73: 451, 1957.
18. Uhlmann, C.H., Kruger, G.R.F., Sesterhenn, K., Rose, K-G., Ablashi, D.V., Wustrow, F.: Nasopharyngeal and Adjacent Neoplasms: A Clinicopathologic and Immunologic Study. *Arch. Otorhinolaryngol.* 218: 163, 1978.
19. Clinical Oncology for Medical Students and Physicians: A Multidisciplinary Approach, 5th Ed. Rubin, P., Editor. American Cancer Society, 1978.
20. Dr. M.E. Blackstein, personal communication.

Together, we can make his world a whole lot safer.

Today, you help him through life's little hurts. Just as you did with his mom when she was growing up.

Now, you can help him to be free of fear from one of life's big hurts by giving generously to the Canadian Cancer Society in your Will.

It's simple and easy. But the results are heartwarmingly effective.

Strides are being made in the fight against cancer, and your bequest will ensure that important but expensive research will be maintained.

Please make that bequest today. With your Will and our way... together we can make their world a whole lot safer.

CANADIAN CANCER SOCIETY

ONCOLOGY

Small Cell Lung Cancer

Part II: A Case Presentation

M.J. Bazos 8T5 and W.K.Evans,* M.D., F.R.C.P. (C)

The projected 2 year survival for patients with limited small cell carcinoma of the lung treated with traditional chemotherapeutic regimens is only 15%. A new approach, Combined Modality Therapy, offers a chance for better survival. Initial induction is with cyclophosphamide, adriamycin, and vincristine (CAV), as well as irradiation to the affected areas. This is followed by a maintenance regimen of lomustine, procarbazine, and methotrexate (CPM). Using this treatment regimen, patient survival into the fifth year from diagnosis has been documented, although it is by no means common. This paper describes the case of one such patient.

History and Physical

A 67 year old caucasian male was admitted to hospital with a history of increasing shortness of breath over the previous year, as well as a two week history of left anterior chest wall pain, non-radiating and constant in nature, accompanied by hemoptysis.

On functional enquiry he denied any recent weight loss, or symptoms of cardiac disease. There was, however, a history of gastroesophageal reflux manifest as postprandial epigastric pain, which was relieved by taking antacid. Two weeks prior to his admission there had been an isolated episode of melena, however, this did not recur. Social history revealed that he had smoked a total of 24 pack-years but had quit smoking 8 years ago.

Physical examination of the chest was normal by inspection, palpation, percussion, and auscultation. There was no cyanosis or clubbing, and cervical and supraclavicular lymphadenopathy was not palpated. The remainder of the physical exam was essentially normal.

Investigations

Routine blood work was as follows: Hb 12.3 gm/dl; WBC 8,500./mm^3 with a normal differential; platelets 630,000/mm^3. Liver function tests were normal: SGOT 27 I.U./ml; ALP 47 I.U./ml.

* *Goldie Rotman Oncology Clinic, Toronto General Hospital, Toronto, Ontario, M5G 1L7*

An X-ray of the chest revealed a large left-sided mass originating in the hilar area and extending into the left upper lung field (Figs. 1, 2). The left paratracheal nodes were noted to be enlarged, and a coin lesion measuring 1.7 cm in diameter was noted in the right basal area.

Figures 1 and 2: Chest roentgenogram, PA and left lateral respectively. Observe the left perihilar mass ill-defined and spreading peripherally into the lung tissue. The mass measures approximately 6 cm in diameter. There is a pleural thickening in the right minor fissure. A second nodule lobulated in appearance and measuring 1.7cm in diameter is noted in the lateral aspect of the right lower lobe. No calcification is detected within either nodule. No skeletal lesions of the chest were noted.

A liver-spleen scan demonstrated irregular uptake of the radionuclide, consistent with hepatic metastasis, and a bone scan and bone marrow were both normal.

Bronchoscopy carried out during an earlier admission failed to obtain a specific tissue diagnosis.

Course in Hospital

Almost immediately upon admission this patient suffered a massive upper GI bleed. At surgery, the cause was found to be a large 3x4 cm benign gastric ulcer located over the lesser curvature of the stomach. This was oversewn to stop the bleeding, and a two-thirds gastrojejunostomy (Bilroth II) was performed. While under the same anaesthetic, a bronchoscopy and brush biopsy confirmed the diagnosis of anaplastic small cell carcinoma of the lung (SCCL). Postoperatively, the patient's course was complicated by a deep-seated wound infection which required re-opening of the entire incision. This was treated with the usual antibiotics and allowed to heal by secondary intention.

Chemotherapy I

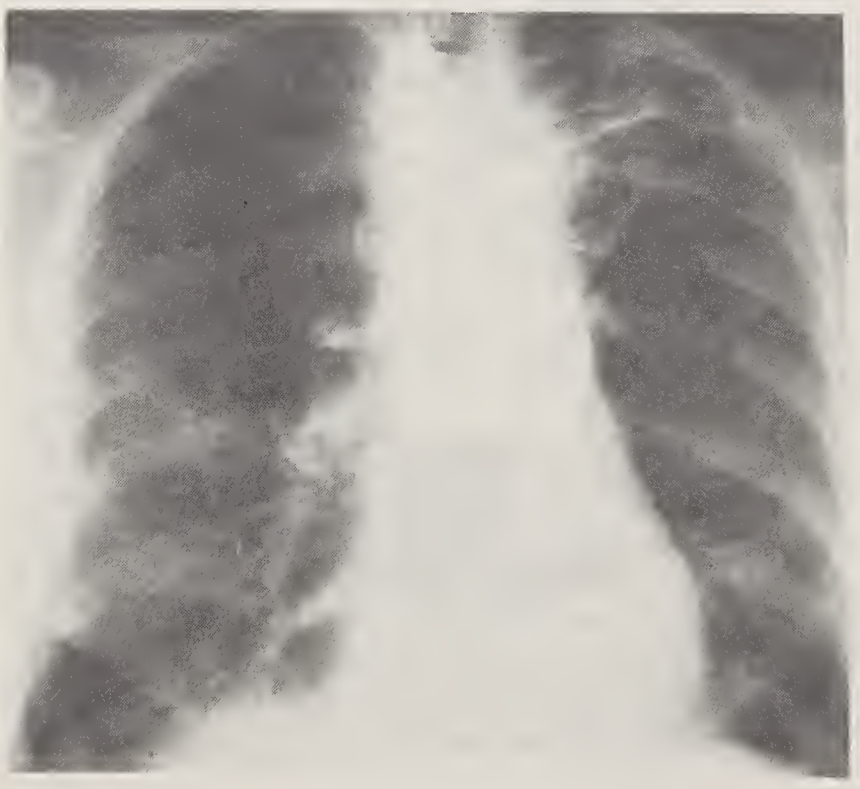
Three weeks post-operatively he received his first dose of combination chemotherapy: adriamycin 70 mg/I.V., cyclophosphamide 1,100 mg/I.V., and vincristine 2 mg/I.V. These three agents in combination have been shown to cause tumor regression in better than 50% of patients with SCCL. [1] Unfortunately, these drugs have many serous side effects which include nausea and vomiting, alopecia, and myelosuppression. [3]

Complications from Induction Therapy

One week later the patient's white cell count dropped to 800/mm^3 and he was running a temperature of 39°C. He was also experiencing nausea, vomiting, and orthostatic hypotension. he was immediately re-admitted to hospital where a Gram stain of his infected wound revealed numerous Gram-positive cocci which on culture grew *Staph. aureus, Strep. viridans,* and anaerobes. The patient was started on intravenous cloxacillin and gentamicin, and remained febrile until five days after admission. A sudden drop in temperature at that time was noted to coincide with the drainage of a large amount of pus from his wound, and it was felt that there had been a small superficial abscess which had spontaneously drained. He remained afebrile for 48 hours, after which he was transfused with two units of blood and discharged with a white cell count of 2,800/mm^3, Hb 8.7 gm/dl, and a platelet count within normal limits.

Chemotherapy II

Eighteen days later he was re-admitted for his second course of combination chemotherapy, and again after three weeks. On both of these occasions the drug dosages were reduced considerably, and he did not experience any further episodes of myelosuppression. Radiologically, there had been a dramatic improvement. The tumor mass before treatment measured 8.5 cm in maximum diameter (Figs. 1, 2), but after only two courses of chemotherapy, the tumor was no longer visible (Figs. 3, 4).



THE UNIVERSITY OF TORONTO

MEDICAL BOOKSTORE

Textbooks for all subjects.

Comprehensive reference books and general interest titles.

Complete review manuals in Medicine and Nursing.

- ask for our free catalogue
- no-charge student charge accounts
- free special order service

The Medical Bookstore is open
Monday through Friday 8:45 am til 6 pm
Saturday from 11 am til 5 pm

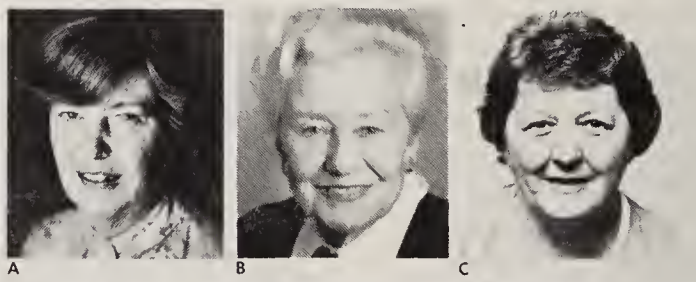
THE MEDICAL BOOKSTORE
is located in
THE UNIVERSITY BOOKROOM
63A St. George Street, Toronto
978-6161

Need Medical Supplies?

WHITE CROSS

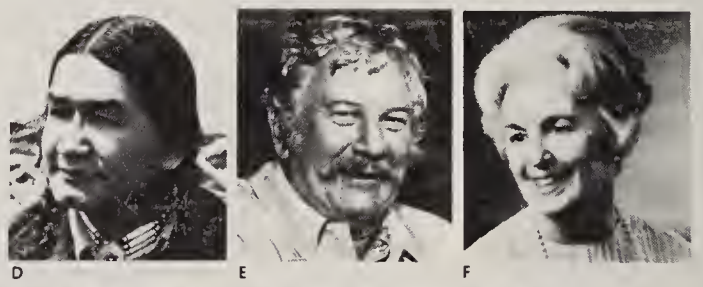
A step in the right direction.

WHITE CROSS
Surgical Instruments Limited
241 Richmond St. West,
Toronto, Ontario M5V 2W3
Tel: (416) 598-4567
Toll Free: 1-(800)-268-9403
(Ontario Only)



A B C

Get involved with UNICEF . . .



D E F

You'll be in good company.

UNICEF VOLUNTEERS: *A Joan Read / Educator, Cobourg B Jean Arnold Tory / Founder UNICEF Canada C Jean Stairs / Homemaker, Fredericton, N.B. D Allen Sapp / Artist, North Battleford E Peter Ustinov / Actor (UNICEF Goodwill Ambassador) F Gertrude Elton / President UNICEF Canada, St. John's, Nfld.*

Unicef Canada

443 Mount Pleasant Road, Toronto, Ont. M4S 2L8
Volunteer Toll Free Number: 1-800-268-6362
(In B.C., 112-800-268-6362) Operator 521.

Creative Concept – Whitehead, Titherington & Bowyer Limited, Advertising Agency.
Art Studio – Bowyer Studios.
Photostats – Canadian Reproduction Company.
Typesetting – Shervill-Dickson Typesetting Limited.
Offset Film – Bomac Batten Limited.
Offset Film – Graphics Diversified Limited

Figures 3 and 4: Chest X-ray, PA and left lateral respectively. There has been significant change since the previous films (figs. 1 and 2). There is considerable scarring surrounding the left hilus which is elevated. There are a number of sub-apical blebs and bullae on the left side; presumably due to irradiation of the left upper lobe region. On the right side, there is a moderately well defined pulmonary nodule in the right lower lobe about 1 1/2 cm in diameter. There are some small subapical blebs and scarring on the right side.

Radiation Therapy

The patient was referred to the Princess Margaret Hospital for a course of radiotherapy consisting of ten treatments (one per day) for a total dose of 2500 rads to the left hilum and mediastinum to consolidate the gains made by the chemotherapy. It must be realized that a complete remission after therapy simply means that the tumor has regressed below the detectability limit of about 10^8 cells: this probably represents a cell-kill of only one or two logs of tumor, leaving a large number of tumor cells capable of initiating a local recurrence. [4]

Follow-up Examination

General physical examination revealed no evidence of recurrent disease. Specifically, the chest was clear and there was no supraclavicular lymphadenopathy.

Chest X-ray showed a complete response with no evidence of the left hilar mass previously present (Figs. 3, 4). The liver was not palpable and there was no bone tenderness.

Maintenance Chemotherapy

After completion of radiotherapy, the patient was placed on maintenance chemotherapy consisting of lomustine (CCNU) 70 mg/I.V., procarbazine 150 mg/I.V., and methotrexate 15mg/I.V. These drugs all have activity against SCCL, but are also myelosuppressive and may cause mild nausea. [5] In addition, methotrexate can cause painful mucositis. The CCNU is given every six weeks and usually causes nausea and vomiting when it is taken. The procarbazine also tends to cause nausea, vomiting and, in some people, severe depression.

Complications from Maintenance Chemotherapy

After six weeks of maintenance chemotherapy the patient developed mucosal bleeding and petachiae all over his body. He had a pancytopenia with Hb 8.2 gm/dl, WBC 1,600/mm^3 and a platelet count of 25,000/mm^3. He was immediately hospitalized.

Physical examination revealed a pale, cachectic looking elderly man in no acute distress with bilateral basal crepitation. The liver was palpable 4 cm below the costal margin, with a total span of 11 cm.

Course in Hospital

The patient was transfused with three units of packed cells, and six units of platelet concentrate.

He was placed on six weekly cycles of maintenance chemotherapy consisting of 50 mg CCNU, and 5 mg methotrexate p.o. twice weekly; and Procarbazine 50 mg daily for ten days. These dosage reductions were necessitated by the severe leukopenia, thrombocytopenia, and mucositis which he experienced six weeks earlier.

The patient continued to do well on maintenance chemotherapy one year from his initial diagnosis. He experienced several episodes of flu-like illness, progressing to a mild pneumonitis, however, both of these problems resolved spontaneously. As a consequence of these infections he was unable to take his oral maintenance chemotherapy, and I.V. therapy had to be substituted.

Long Term Follow-up

He remained off his maintenance chemotherapy for eighteen months during which time he returned every six weeks for follow-up examination. During this time he remained well and his physical examination continued to be unremarkable.

Two months later, the patient was hospitalized complaining of acute onset of pleuritic substernal chest pain. he was found to be in atrial fibrillation with a ventricular rate of 110-120/min and a radial pulse of approximately 80-90/min. He was placed on digoxin 0.25 mg daily, which after three weeks relieved him of his cardiac symptoms.

As far as his neoplasm was concerned, there was no evidence of tumor recurrence as he approached his two year mark.

The patient returned every three months for nearly one year virtually symptom free with the exception of intermittent hoarseness. An ENT examination revealed a laxity of the vocal cords. Such bowing of the vocal cords is frequently seen in this age group, but an additional lag in the left cord was thought to be related to post-irradiation mediastinal scarring with traction on the recurrent laryngeal nerve. There was no evidence of a local malignancy in the pharyngo-laryngeal area.

He remained in complete remission on his third anniversary since initial chemotherapy. During his quarterly visits he con-

tinued to do well and was free of symptoms. Physical examination revealed no evidence of recurrent disease, and except for persistent atrial fibrillation, was unremarkable.

Cardiovascular Complications

Approximately four years from the start of his treatment this patient suffered a myocardial infarction complicated by transient papillary muscle dysfunction. He made a complete recovery by six months.

Review of his chest X-rays demonstrated scarring in the left lung apex with elevation of the left hilum possibly due to radiation-induced fibrosis of the surrounding area (Figs. 3, 4). A calcified lesion in the right lower lobe noted on previous films had not undergone any change, and it was felt that this might represent a healed granuloma.

He is currently being followed at six month intervals, and continues to do well five years since his initial diagnosis. □

Acknowledgements

This paper was supported by a Terry Fox Cancer Research Clerkship Award from the National Cancer Institute of Canada. The author would like to thank Dr. W.K. Evans of the Toronto General Hospital for his assistance in the preparation of the manuscript.

References

1. Feld, R., Pringle, J.F., Evans, W.K., et al.: Combined Modality Treatment of Small Cell Carcinoma of the Lung. *Arch Inter Med.*, 141: 469-473, 1981.
2. Bunn, P.A. Jr., Nugent, J.L., Mathews, M.J.: Central nervous system metastases in small cell bronchogenic carcinoma. *Semin Oncol.*, 5: 314-322, 1978.
3. Bazos, M.J., Evans, W.K., Wang, P.Y., Drakos, T.T.: Small Cell Lung Cancer — I. A Curable Disease. *Univ. Toronto Med. J.* 60: 19-22, 1982.
4. Denekamp, J.: Cell Kinetics and Cancer Therapy: *Human Tumour Kinetics*. Charles C. Thomas, publ., Illinois, USA, pp. 61-62, 1982.
5. Feld, R.: Complications in the treatment of small cell carcinoma of the lung. *Cancer Treatment Rev.*, 8: 5-25, 1981.

REVIEW ARTICLE

Two Pathways of T-cell Mediated Immune Tolerance of the IgE System

W. David Colby, M.Sc. 8T4

When Immunology was in its infancy, investigators were concerned with the enhancement of the immune response to cure infections. Today, the prevention or elimination of an immune response is also considered to be very important. "Immune Tolerance" refers to a state of unresponsiveness encountered in situations where immunity would normally occur. Tolerance (also known as protein overloading, paralysis, and unresponsiveness), like immune induction, represents a fundamental mechanism and therefore is important to the understanding of the immune system from both a basic and a clinical perspective. Experimental tolerance often mimics the tolerance that animals have to their own tissue antigens. The understanding of tolerance is essential for tissue transplantation and for the treatment of allergy and autoimmune diseases.

Most concepts of tolerance are based on F.M. Burnet's clonal selection model.[6]

> It assumes that in the animal there exist clones of mesenchymal cells, each carrying immunologically reactive sites corresponding in appropriate complementary fashion to one (or possibly a small number of) potential antigenic determinants. This provides a population of cells which, when an appropriate stage of development has been reached, are capable of producing the population of globulin molecules which collectively provide the normal antibodies. When an antigen is introduced it will make contact with a cell of the corresponding clone, presumably a lymphocyte, and by so doing, stimulate it to produce in one way or another more globulin molecules of the cell's characteristic type. The obvious way of achieving this is to postulate that stimulation initiates proliferation as soon as the cell in question is taken into an appropriate tissue niche, spleen, lymph node, or subacute inflammatory accumulation.

Since all of the immunosuppressive agents and procedures are preferentially toxic to dividing cells, clones expanding in response to antigenic stimulation are particularly vulnerable to elimination. This is termed "clonal deletion". Burnet postulated that all autoreactive clones are eliminated, both during and subsequent to embryonic life.

Two types of lymphocytes, the T-cell and the B-cell (plus the macrophage), must cooperate to achieve an antibody response to most antigens.[48,33] Unresponsiveness can be achieved by blocking the contribution of any one of these cell types. Depending on the experimental conditions, either T- or B-cell tolerance can be induced without necessarily involving the other cell type. In the case of hapten-carrier conjugates, tolerance induction to the carrier abrogates the antibody response to a hapten coupled to the same carrier.[19,39] This type of tolerance operates exclusively via T-cells, since in adoptive transfer experiments T-cells from tolerant animals fail to provide the helper function, while B-cells from similarly treated donors are capable of producing anti-hapten antibodies in collaboration with normal or carrier-primed T-cells.[19,40] B-cell tolerance can also be produced without T-cell involvement in systems using T- independent antigens.

An interesting variant of the clonal deletion model is the "clonal abortion" model proposed by Nossal and Pike. [35] They postulate the existence of a phase of B- lymphocyte differentiation when the antigen-specific but immature lymphocytes can be permanently eliminated or inactivated if they are exposed to antigen in the proper concentration. Tolerance would develop whenever antigen is present before lymphocytes are developed, which would ensure that tolerance to self antigens prevails.

In addition to the mechanisms of clonal deletion and clonal abortion already discussed above, several other mechanisms have been proposed to explain the phenomenon of immune tolerance: antibody-mediated tolerance,[5] receptor blockade[1] and the effect of suppressor T-cells.[18]

Suppressor cells which are capable of interfering with the collaboration between helper T-cells and B-cells, were postulated separately by Baker et al[3] and by Gershon and Kondo.[17] More than one of these mechanisms may take place concurrently or sequentially, as demonstrated by Claman et al[11] in studies of delayed hypersensitivity to DNFB in the mouse. These investigators found that donors tolerized (and demonstratably so) to DNFB by intravenous injection of $DNBSO_3$ could transfer tolerance to naive recipients one week later by adoptive transfer of spleen cells. However, equally tolerant donors tolerized two weeks or two days in advance could not transfer tolerance. Claman and associates postulated that two distinct mechanisms of negative immunoregulation were in effect, one involving receptor blockade and one dependent on suppression cells.

Extended dosage schedules of small amounts of antigen seems to favour suppressor T-cell induction,[20,27,49] indicating that suppressor cells respond with immunological memory.[15,32] As well, suppressor T-cells may be important in the stability and maintenance of tolerance.[4] Alternatively, tolerance can be present in mice when suppressor cells cannot be demonstrated.[11,16] A recent paper has implied that neonatal tolerance is easily induced due to large numbers of suppressor cells in newborns.[38]

In summary, immune tolerance is dependent upon several factors. These are the nature (i.e. immunogenicity) of the antigen, the dose of the antigen, the route of administration, and the immunocompetence of the animal. Implicit in the last factor are the species, strain, age, and physical condition of the animal. Although both T- and B-cells are required for most responses to antigen, both cell groups can be made tolerant independently and show different kinetics[8,47]. Tolerance may involve cells which suppress T-cell and B-cell collaboration (suppressor cells). Termination of tolerance may occur spontaneously, or upon immunization of the animal with a cross-reacting compound[10,14,34,37,50,55,57].

As in other immunoglobulin classes, both positive and negative regulation of the IgE antibody response depends upon the collaboration between T- and B-derived lymphocytes and macrophages, except that the IgE response is strictly T-dependent[24]. However, regulatory interactions have been recognized to operate for the IgE antibody response which have not been encountered in the study of other immunoglobulin classes. Among these are the enhanced IgE antibody reproduction follow low does of X-irradiation, adult thymectomy, or administration of immuno-suppressive drugs[9,45], the selective modulatory effect of adjuvants,[25,27,44] and the exceedingly high susceptibility to antingen-specific[45] and non-specific[26] T- lymphocyte derived suppressor molecules.

Antigen-induced tolerance of the IgE system seems to operate along two basic patterns. The first is obtained following the administration of a single large dose of deaggregated heterologous IgG[41,42] or of multiple low doses of native, deaggregated or chemically modified antingen[31,43,46]. All of these treatments are associated with the product of T-suppressor cells. The second pattern is observed after the administration of polyvalent penicilloyl-amino acid polymers[36], or of haptens conjugated to homologous immunoglobulin[29,30]. This is believed to operate via B-cell receptor blockade.

Studies by Sanfilippo and Scott[41,42] have shown that rats pretreated with a single large dose (10 mg) of deaggregated sheep gammaglobalin became tolerant to both carrier and hapten (2, 4, 6-trinitrophenyl, TNP), and suggested the existence of a dual mechanism, one operating via T-suppressor cells and the other by direct unresponsiveness of T-helper cells. Similar suggestions have been made previously to explain the patterns of unresponsiveness to self antigens[2] and to heterologous serum proteins[56]. Cohn and Scott[12] have demonstrated that T-helper cell precursors from the bone marrow of rats can be rendered tolerant with respect to IgG antibody production by a single injection of tolerogen (deaggregated sheep gamma globulin). This tolerance had a rapid rate of reversal and was not due to T-suppressor cells.

Colby and Strejan[13] have recently demonstrated by adoptive transfer the presence of a tolerant population of spleen cells of thymic origin in CBA mice pretreated with deaggregated ovalbumin (dOA). These tolerized T-cells were unable to interfere in the normal collaboration between carrier-primed helper cells and IgE antibody-forming cell precursors. However, under conditions of prolonged donor pretreatment with both tolerogenic (dOA) and immunogenic (native OA in alum) forms of antigen, T-suppressor cells were demonstrated. This led the authors to suggest that conditions favourable to the generation of T-suppressor cells are created after a single tolerizing dose of antigen, but that subsequent repeated stimulation by immunogenic forms of the antigen is required to expand the suppressor T-cell clones to a detectable level.

Recall of antigen-specific suppressor cell activity has been shown to occur both *in vivo*[32] and *in vitro*[5]. The hypothesis has also been supported by the recent work of Holt and Leivers[21], who demonstrated IgE specific tolerance after challenge with immunogenic alum-adsorbed OA in Balb/C

mice which had been exposed to aerosolized OA once weekly for 6 weeks. Pretreated mice which were challenged instead with a less immunogenic soluble OA mounted an anamnestic IgE response initially, but tolerance was established after a second challenge with soluble OA 13 days after the first challenge. These authors did not observe dissociation between tolerance and T-suppressor cell activity. This might be explained by the high IgE response of Balb/C mice as compared to the CBA mice used by Colby and Strejan. It is also possible that T-suppressor cells might have been present but in numbers too small to be detected. If, however, one accepted the supposition that T-cell tolerance was exclusively a function of T-suppressor cell activity, it would be difficult to explain the fact that a functionally unresponsive helper cell population was incapable of interfering with the development of an antibody response after adoptive transfer.

Taken collectively, evidence is accumulating that suppressor cells are but one of at least 2 distinct and not necessarily coexistant mechanisms of T-cell mediated IgG and IgE tolerance. It is not clear at the present time whether non-suppressor T-cell tolerance is due to deletion of tolerized T-cell clones or to reversible T-cell receptor blockade. □

References

1. Aldo-Benson, M. and Y. Borel: The tolerant cell: Direct evidence for receptor blockage by tolerogen. *J. Immunol. 112:* 1793-1803, 1974.
2. Allison, A.C., A.M. Denman and R.D. Barnes: Cooperating and controlling functions of thymus-derived lymphocytes in relation to autoimmunity. *Lancet 2:* 135-140, 1971.
3. Baker, P.J., R.W. Stashak, D.F. Amsbaugh, B. Prescott and R.F. Barth: Evidence for the existence of two functionally distinct types of cells which regulate the antibody response to Type III pneumococcal polysaccharide. *J. Immunol. 105:* 1581-1583, 1970.
4. Benjamin, D.C.: Evidence for specific suppression in the maintenance of immunologic tolerance. *J. Exp. Med. 141:* 635-646, 1975.
5. Birnhaum, G., M.E. Weksler and G.W. Siskind: Demonstration of an antibody-mediated tolerance state and its effect on antibody affinity. *J. Exp. Med. 141:* 411-426, 1975.
6. Burnet, F.M.: *The Clonal Selection Theory of Acquired Immunity.* Vanderbilt Univ. Press, Nashville, Tenn. p. 54, 1959.
7. Bussard, A.: Formation d'auto-anticorps anti-erythrocytes consecutive a une immunisation croisee chez le lapin. In: *La greffe des cellules hematopoietiques allogeniques.* p. 157-167 (Ed CNRS, Paris), 1965.
8. Chiller, J.M., G.S. Habicht and W.O. Weigle: Kinetic differences in unresponsiveness of thymus and bone marrow cells. *Science 171:* 813-815, 1971.
9. Chiorazzi, N., D.A. Fox and D.H. Katz: Hapten-specific IgE antibody in mice VI. Selective enhancement of IgE antibody production by low doses of X-irradiation and by cyclophosphamide. *J. Immunol. 117;* 1629-1637, 1976.
10. Cinader, B. and J.M. Dubert: Acquired immune tolerance to human albumin and response to subsequent injections of diazo human albumin. *Brit. J. Exp. Pathol. 36:* 515-529, 1955.
11. Claman, H.N., S.D. Miller and J.W. Moorhead: Tolerance: Two pathways of negative immunoregulation in contact sensitivity to DNFB. *Cold Spr. Harb. Symp. Quant. Biol. 41* (1): 105-111, 1976.
12. Cohn, M.L. and D.W. Scott: Functional differentiation of T cell precursors I. Parameters of carrier-specific tolerance in murine helper T cell precursors. *J. Immunol: 325:* 2085-2087, 1979.
13. Colby, W.D. and G.H. Strejan: Immunological tolerance of the mouse IgE system: dissociation between T cell tolerance and suppressor cell activity. *Eur. J. Immunol. 10:* 602-608, 1980.
14. Cox, K.O. and D. Keast: Erythrocyte autoantibodies induced in mice immunized with rat erythrocytes. *Immunology 25:* 531-539, 1973.
15. Eardley, D.D. and E.E. Sercarz: Recall of specific suppression: Co-dominance of suppression after priming or secondary antigen stimulation. *J. Immunol. 118:* 1306-1310, 1977.
16. Fujiwara, M. and A. Kariyone: Incidental appearance of suppressor T-cells in the induction of immunological tolerance. *Immunology, 34:* 51-56, 1978.
17. Gershon, R.K. and K. Kondo: Cell interactions in the production of tolerance: the role of thymic lymphocytes. *Immunology 18:* 723-737, 1970.
18. Gershon, R.K. and K. Kondo: Infectious immunological tolerance. *Immunology 21:* 903-914, 1971.
19. Green, I., W.E. Paul, and B. Benacerraf: Hapten carrier relationships in the DNP-PLL foreign albumin complex system: induction of tolerance and stimulation of cells *in vitro. J. Exp. Med. 127:* 43-53, 1968.
20. Heuer, J., R. Stumpf, E. Kolsch, F-W. Shen and G.J. Hammerling: Suppressor T cells in low zone tolerance II. Characterization of suppressor T and amplifier cells by physical and serological methods. *Eur. J. Immunol. 7:* 769-775, 1977.
21. Holt, P.G. and S. Leivers: Tolerance induction via antigen inhalation: isotype specificity, stability, and involvement of suppressor T cells. *Int. Arch. Allergy appl. Immunol. 67:* 155-160, 1982.
22. Howard, J.G., G.H. Christie, B.M. Courtenay, E. Leuchars and A.J.S. Davies: Studies on immunological paralysis VI. Thymic-independence of tolerance and immunity to type III Pneumococcal polysacchride. *Cell. Immunol. 2:* 614-626, 1971.
23. Howard, J.G. and N.A. Mitchison: Immunological tolerance. *Progr. Allergy 18:* 43-96, 1975.
24. Ishizaka, K.: Cellular events in the IgE antibody response. *Adv. Immunol. 23:* 1-75, 1976.
25. Katz, D.H. and A.S. Tung: Regulation of IgE antibody production by serum molecules II. Strain specificity of the suppressive activity of serum from complete Freund's adjuvant-Immune low responder mouse donors. *J. Immunol. 120:* 2060-2067, 1978.
26. Kishimoto, T., Y. Hirai, M. Suemura, K. Nakanishi and Y. Yamamura: Regulation of antibody response in different immunoglobulin classes IV. Properties and functions of "IgE class-specific" suppressor factor(s) released from DNP-Mycobacterium primed T cells. *J. Immunol. 121:* 2106-2112, 1978.
27. Kishimoto, T. and K. Ishizaka: Regulation of antibody response *in vitro* VI. Carrier-specific helper cells for IgG and IgE antibody responses. *J. Immunol, 111:* 720-732, 1973.
28. Kolsch, E., R. Stumpf and G. Weber: Low zone tolerance and suppressor T-cells. *Transpl. Rev. 26:* 56-86, 1975.
29. Lee, W.Y. and A.H. Sehon: Suppresion of reaginic antibody formation II. The use of adoptive transfer. *J. Immunol. 114:* 837-842, 1975.
30. Lee, W.Y. and A.H. Sehon: Suppression of reaginic antibody formation IV. Suppression of reaginic antibody to penicillin in the mouse. *J. Immunol. 117:* 927-934, 1976.

31. Lee, W.Y. and A.H. Sehon: Abrogation of reaginic antibodies with modified allergens. *Nature, 267:* 618-619, 1977.

32. Loblay, R.H., H. Pritchard-Briscoe and A. Basten: Suppressor T-cell memory. *Nature, 272:* 620-622, 1978.

33. Mitchison, N.A.: In *Immunological Tolerance* (M. Landy and W. Braun, eds.) page 149, Academic Press, New York, 1969.

34. Nakamura, R.M. and W.O. Weigle: Suppression of thyroid lesions in rabbits by treatment with cyclo-phosphamide after the induction of thyroiditis. *Clin. Exp. Immunol. 7:* 541-550, 1970.

35. Nossal, G.J.U. and B.L. Pike: Evidence for the clonal abortion theory of B-lymphocyte tolerance. *J. Exp. Med. 141:* 904-917, 1975.

36. Otz, U., C.H. Schneider, A.L. deWeck, E. Gruden and T.J. Gill: Induction of immunological tolerance to the penicilloyl antigenic determinant I. Evolution of penicilloylated amino acid polymers and copolymers in mice. *Euro. J. Immunol. 8:* 406-410, 1978.

37. Playfair, J.H.L. and S. Marshall-Clarke: Induction of red cell autoantibodies in normal mice. *Nature New Biol. 243:* 213-214, 1973.

38. Ptak, W., K.F. Naidorf, J. Strzyzewska and R.K. Gershon: Ontogeny of cells involved in the suppressor circuit of the immune response. *Euro. J. Immunol. 9:* 495-500, 1979.

39. Rajewsky, K., E. Rottlander, G. Peltre and B. Muller: The immune response to a hybrid protein molecule. Specificity of secondary stimulation and of tolerance induction. *J. Exp. Med. 126:* 581-606, 1967.

40. Sanfilippo, F. and D.W. Scott: Cellular events in tolerance III. Carrier tolerance as a model for T cell unresponsiveness. *J. Immunol. 113:* 1661-1667, 1974.

41. Sanfilippo, F. and D.W. Scott: Carrier-specific unresponsiveness in reaginic antibody formation I. Induction of helper cell tolerance in rats. *Cell. Immunol. 28:* 427-436, 1977.

42. Sanfilippo, F. and D.W. Scott: Carrier-specific unresponsiveness in reaginic antibody formation II. Suppression of hapten and carrier responsiveness in presensitized rats. *Cell. Immunol. 28:* 435-442, 1977.

43. Sauerbronn-Maia, L.C., N.M. Uaz and E.M. Vaz: Effect of soluble antigen on IgE responses in the mouse. *Int. Arch. Allergy, 46:* 339-344, 1974.

44. Strejan, G.H., K. Rabheru, R. White and D. Surlan: Reaginic antibody production to *Ascaris suum* allergen ASC-; II. Influence of type of adjuvant and of carrier priming on the induction of IgE and IgG antibody to dinitrophenyl conjugates. *Int. Arch. Allergy, 54:* 502-516, 1977.

45. Tada, T: Regulation of reaginic antibody formation in animals. *Prog. Allergy, 19:* 122-194, 1975.

46. Takatsu, K. and K. Ishizaka: Reaginic antibody formation in the mouse VI. Suppression of IgE and IgC antibody responses to ovalbumin following the administration of high dose urea-denatured antigen. *Cell Immunol. 20:* 276-289, 1975.

47 Taylor, R.B.: Immune paralysis of thymus cells by bovine serum albumin. *Nature 220:* 611, 1968.

48. Taylor, R.B.: Cellular cooperation in the antibody response of mice to two serum albumins. Specific function of thymus cells. *Transpl. Rev. 1:* 114-149, 1969.

49. Weber, G. and E. Kolsh: Transfer of low zone tolerance to normal syngeneic mice by 0 positive cells. *Euro J. Immunol. 3:* 767-772, 1973.

50. Weigle, W.O.: The immune response of rabbits tolerant to bovine serum albumin to the injection of other heterologous serum albumins. *J. Exp. Med. 114:* 111-125, 1961.

51. Wigle, W.O.: Termination of acquired immunological tolerance to protein antigen following immunization with altered protein antigens. *J. Exp. Med. 116:* 913-928, 1962.

52. Weigle, W.O.: The production of thyroiditis and antibody following injection of unaltered thyroglobulin without adjuvant into rabbits previously stimulated with altered thyroglobulin. *J. Exp. Med. 122:* 1049-1062, 1965.

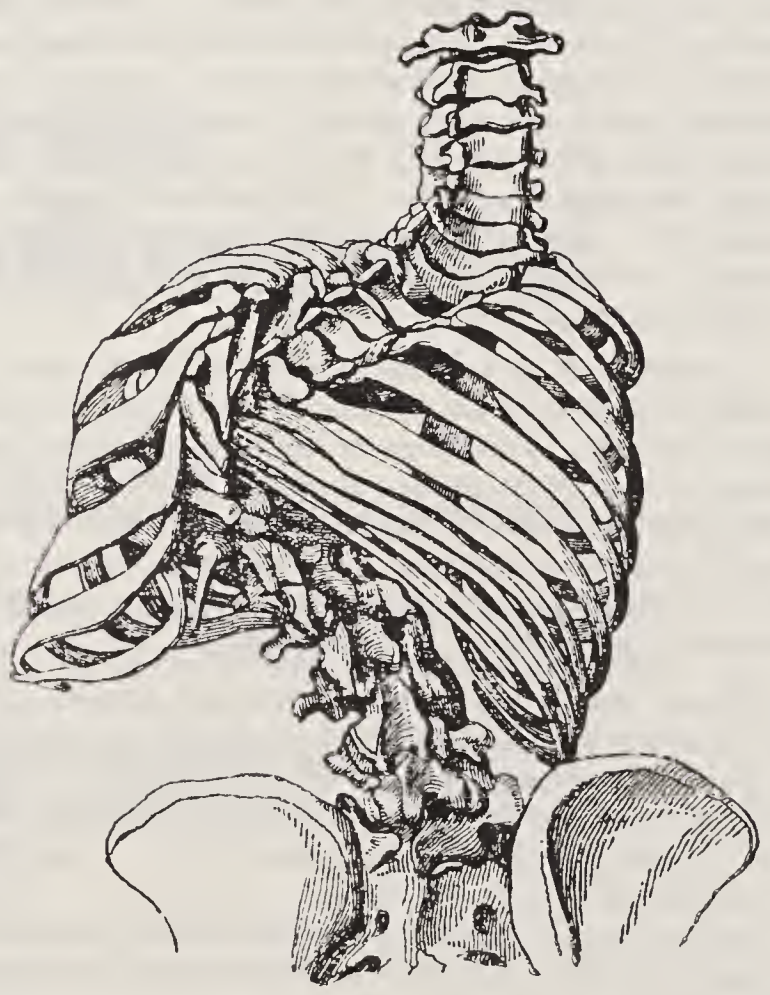
53. Weigle, W.O.: The induction of autoimmunity in rabbits following injection of heterologous or altered homologous thyroglobulin. *J. Exp. Med. 121:* 289-308, 1965.

54. Weigle, W.O.: Immunological unresponsiveness. *Adv. Immunol. 16:* 61-122, 1973.

55. Weigle, W.O. and R.M. Nakamura: The development of autoimmune thyroiditis in rabbits following injection of aqueous preparations of heterologous thyroglobulins. *J. Immunol. 99:* 223-231, 1967.

56. Weigle, W.O., D.G. Sieckmann, M.U. Doyle and J.M. Chiller: Possible roles of suppressor cells in immunological tolerance. *Transpl. Rev. 26:* 186-205, 1975.

57. Yamashita, U., T. Takami, T. Hamaoka and M. Kitagawa: The role of hapten-reactive T-lymphocytes in the induction of autoimmunity in mice II. Termination of self-tolerance to erythrocytes by immunization with hapten-isologous erythrocytes. *Cellular Immunology 25:* 32-40, 1976.



Reproduced from Researches into the Pathology and Treatment of Deformities in the Human Body *by John Bishop, F.R.C.S., Highley and Son, London, 1852. Held in the University of Toronto, Thomas Fisher Rare Book Library.*

BOOK REVIEW

Living and Working with Schizophrenia

M.W.Seeman, S.K. Littman, E. Plummer, J.F. Thorton and J.J. Jeffries
(University of Toronto Press, 1982, $6.95)

Many a survivor of Medical Pharmacology will associate the name Seeman with dopamine and schizophrenia, however, *Living and Working with Schizophrenia* is not about neurotransmitters. It deals, rather, with the 'other' side of this illness, namely the patient, the patient's family, his friends and the community, all of whom must adjust their lives in the face of this illness. The book purports to be a practical sourcebook and reference, providing both basic information on the nature of schizophrenia and its treatment, as well as advice regarding effective means of dealing with difficult situations.

The book has a two-part format. Part I (Basic Information) covers a lot of ground regarding the nature of schizophrenia. It clarifies the roles of the treatment team, describes what is involved in hospitalization and outpatient care, and includes a chapter on drugs and their side-effects. It also outlines how people closely involved with a schizophrenic person can respond creatively to such basic issues as social outings, work, the handling of money, and sexual intimacy.

Despite the layman's orientation, insufficient attention is given to the emotional responses that family and friends might experience. Some brief mention regarding feelings of anger and shame has been made, but the issue of *fear* is not broached, specifically the fear of madness and of social stigma. Clearly, this is a major factor colouring the reaction of us all — family, friends, and medical students — in dealing with a mentally ill person. In a handbook designed to assist the layman in adjusting constructively to daily life with an ill person, this could be viewed as a serious omission.

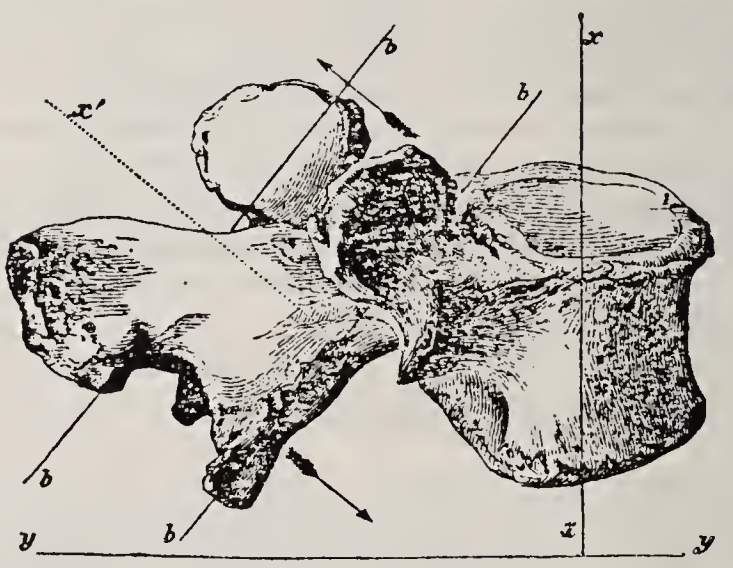
It is difficult to try to imagine reading this book from the viewpoint of an immigrant shopkeeper, a factory worker, or a miner. To such a reader parts of this book would be hard-going, and some of the phrases mystifying. A welfare mother, unemployed and with four children to care for, might find this book frustrating as it assumes a supportive family unit with the emotional, financial, and spiritual resources needed to cope with a schizophrenic family member.

While an open, supportive approach is taken and efforts are made to emphasize that the affected individual is a *person* with an illness, phrases such as "The schizophrenic is. . .", and "Schizophrenics may become. . ." appear too frequently. One would hesitate to say "The atherosclerotic is. . ." or "The Crohn's disease is. . ."

However, families, friends, and medical students might find that part II justifies the purchase price of the book. In this section parents describe what it feels like to have a schizophrenic child, and recount their frustrations in dealing with psychiatrists, hospital staff, social workers, etc. Patients reflect on the meaning of a diagnosis of schizophrenia and describe how they have come to terms with their illness. For families, this may ease the pain and alienation which can accompany the development of mental illness is a family member. For medical students this describes aspects of mental illness not sufficiently stressed in the medical curriculum.

Would I recommend this book? Yes — to concerned families and to friends who need a handy reference. Clearly, comprehensive solutions to the problem of schizophrenic illness — from the viewpoint of minimizing the social and economic burden for the community, and from the viewpoint of maximizing the life-potential of the mentally ill person — will eventually involve community and family responsibility. We are still far from this goal, but with efforts such as the programme this book grew out of, we become closer. The authors are to be commended for their work in helping us to achieve such an understanding and interpretation. □

Lora Lee Hamilton



Reproduced from Researches into the Pathology and Treatment of Deformities in the Human Body *by John Bishop, F.R.C.S., Highley and Son, London, 1852. Held in the University of Toronto, Thomas Fisher Rare Book Library.*

Compliments of
BURROUGHS WELLCOME

"Research is our only stockholder"

BURROUGHS WELLCOME INC.
LASALLE, QUÉ., CANADA

ALL THE BANKING SERVICES YOU'LL EVER NEED.

- ☐ Daily Interest Savings
- ☐ Blue Chip Savings
- ☐ Scotia Chequing
- ☐ Scotia Plan Loans
- ☐ Scotiabank Visa
- ☐ Scotiabank Hockey College
- ☐ Scotiaclub
- ☐ Scotia 59 ers
- ☐ Safety Deposit Boxes
- ☐ Safekeeping
- ☐ Travellers Cheques
- ☐ Money Orders
- ☐ Foreign Exchange
- ☐ Gold and Gold Certificates

Besides all that, we like people. And we'd like to know you. Drop in soon, won't you?

Scotiabank®
THE BANK OF NOVA SCOTIA

Our three major commitments

To the past: **the continuation of high standards of achievement**

To the present: **providing excellent products with service to the medical community.**

To the future: **investing in research for the further preservation of health and life.**

We are
Geigy Pharmaceuticals

NUTRITION AND MEDICINE

Dietary Fiber and Colon Cancer: Is There a Link?

Ruth M. Kay, Ph.D. 8T4

Dietary fiber is only one of several dietary variables tentatively implicated in the etiology of large bowel cancer. Epidemiological studies in Denmark[1], Finland[1,2], United States[2], Israel[3], and England[4] have demonstrated inverse relationships between fiber intake and colon cancer incidence. However in many cases, the diets also differed in other respects including fat, lactose and indole content. Similarly although there is evidence that wheat bran and similar fibers may reduce tumor formation in animals, the applicability of animal models of chemically induced carcinogenesis to human cancer is unclear[5]. These studies have been reviewed in detail elsewhere[6].

Fiber exerts a number of actions in the large bowel which may be postulated to mitigate against tumorigenesis. These include effects on fecal concentration of mutagens and co-carcinogens, alteration in intestinal transit, changes in the chemical environment of the right colon with attendant alterations in the metabolic activity of intestinal flora and direct or indirect effects on mucosal cell turnover and epithelial morphology.

Effects on Concentration of Tumor-Active Agents

Most types of dietary fiber have a significant effect on stool bulk and water content. This effect is likely to be related not only to the hydration capacity of the surviving residue (greatest for coarse particulate fibers such as wheat bran) and production of osmotically active metabolites, but also to the induction of bacterial growth, since bacterial cells are normally 80% water and represent an important fraction of total stool volume[7]. Effects on bacterial volume may explain the reported relationship of fecal weight to intake of one group of fibers, the pentose-containing polysaccharides, since these result in a marked increase in bacterial growht and output[8].

Stool bulking capacity varies depending on the source of the dietary fiber. Although large amounts of fermentable fibers enhance fecal bulk and water content, they are somewhat less effective than the less fermentable types. In a recent study, Stasse-Wolthuis and colleagues[9] demonstrated that the mean increase in stool weight was 4.1 g/g of added fiber for coarse wheat bran (fermentation-resistant) as compared to 1.9 g/g added fiber when fruit and vegetables (highly fermentable) were used as a fiber source.

By increasing stool bulk, dietary fiber dilutes the concentration and hence colonic mucosal contact of specific substances implicated in tumor growth or initiation. Included are a range of compounds including bile acids[10], neutral steroids[11], ammonia[12], nitrosamines[13], and environmental carcinogens such as polycyclic aromatic hydrocarbons. Of particular interest is the effect of dietary fiber on the colonic concentration of bile acids.

Acids sterols have been shown to act as cocarcinogens in animal studies whether ingested[14], rectally instilled[14], surgically diverted through the colon[16], or adsorbed to cholestyramine[17]. The mechanisms by which bile acids enhance colonic carcinogenesis are not well understood. Free bile acids produce a number of biological changes in intestinal mucosal cells[18]. There is evidence that bile acids influence the growth and morphology of cultured human fibroblasts and increase the turnover of intestinal mucosal cells[19]. By acting as mitogens, bile acids may increase the effectiveness of any of a host of mutagenic agents. The secondary bile acids, deoxycholic acid and lithocholic acid, produced by bacterial dehydroxylation of cholic and chenodeoxycholic acids (Figure 1) appear to have greater promoting activity than the corresponding primary bile acids[20]. However, bacterial metabolism of bile salts is not an absolute requirement because tumor enhancement was observed in germ free animals[20]. Hill et al, have demonstrate *in vitro* colonic anerobes of the Clostridia species can, through a series of nuclear dehydrogenation reactions, convert bile acids into carcinogenic phenanthrenes[21],[22]. However, such metabolites have not been isolated *in vivo* and rectal installation of bile acids alone did not result in tumor formation. In certain population studies, the fecal deoxycholate, or total bile acid concentration correlated with the incidence of large bowel cancer[23] as did the ratio of secondary to primary bile acids[16]. However, inconsistencies have been reported[24]. Bacterial strains in the stools of low-risk populations showed a reduced capacity for 7-dehydroxylation of bile acids[25]. In case control studies, colon cancer patients were shown to have higher concentrations of fecal bile acids, increased stool pH, and greater activity of 7-dehydroxylase and cholesterol dehydrogenase enzymes[23].

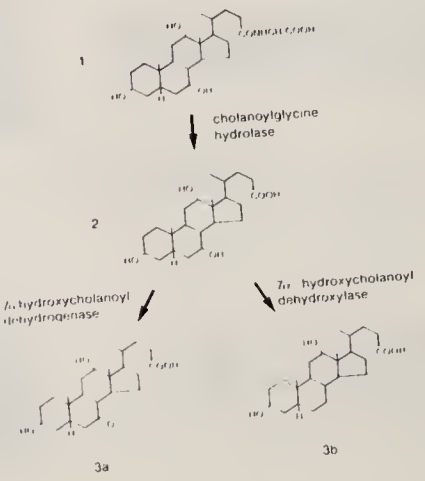
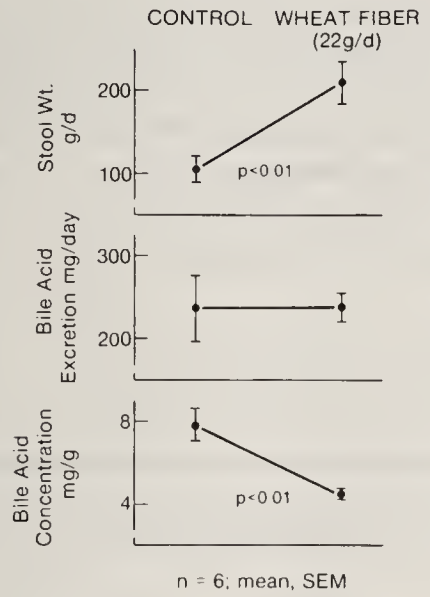


Figure 1. Bacterial modification of bile acids, Hydrolysis of conjugated bile acids (glyco- or tauro-) by cholanoylglycine hydrolase may be followed by 7 -dehydroxylation to yield lithocholate or deoxycholate. Alternatively, the primary bile acids may undergo 7 -hydroxydehydrogenation to give a keto derivative. The latter is a reversible reaction. 1,5-cholanic acid-3,7,12-triol-N-(carboxymethyl) -amide;1,2,5-cholanic acid-3,7,12-triol; 3a,5-cholanicacid-3,12-diol-7-one;3bn, 5-cholanic acid-3,12-diol.

Most types of dietary fiber, by enhancing stool bulk, act to decrease the colonic concentration of bile acids. However, the extent to which a specific fiber reduces fecal bile acid concentration will be modified by its concomitant effect on total sterol excretion. Whereas wheat bran decreased the concentration of bile acids in the stool (Figure 2), more potent sterobinding fibers such as oat bran, lignin, and pectin did not (Figure 3). Although dietary fat intake also influences fecal bile acid concentration, within the normal range of intake (25-45% of calories), the effect is less than that produced by altered fiber intake[26]. In controlled studies, we examined the effect of alteration in dietary fat and fiber intake on plasma lipoproteins and fecal excretion of bile acids. Whereas a decreased in dietary fat intake from 40% to 27% of calories did not alter fecal bile acid concentration, an increase in fiber intake from 20 to 45 g/d resulted in a 50% reduction in this variable[27].



Fibure 2. Wheat fibre does not alter bile acid excretion but does have a profound effect on stool bulk. Thus the concentration of bile acids in contact with the colonic mucosa is significantly decreased[43].

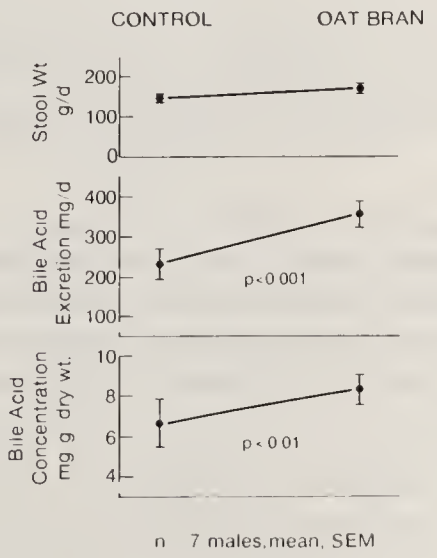


Figure 3. The fibre in oatbran also increases stool bulk but since there is a similar effect on bile acid output, this fiber increases rather than decreases the colonic concentration of bile acid[44].

Table I: Fecal bile acid concentration, pH and enzymatic activity in colorectal cancer patients as compared to control subjects.

		Colorectal Cancer Patients
Hill et al (23)	Fecal Bile Acids	↑
MacDonald et al (34)	Stool pH	↑
Mastromarino et al (25)	7-de OHase	↑
	Chol deHase	↑
	β-glucuronidase	0

Large Bowel Transit-Time

By reducing colonic transit time, dietary fiber may reduce the opportunity for bacterial formation or activation of potential carcinogens. In addition, prompt sigmoid evacuation will shorten the period of contact between tumor-promoting agents and bowel mucosa. Clinical studies have shown that addition of fiber to the diet results in whole gut transit times especially when transit is initially prolonged[7,28].

Alterations in the Chemical Environment of the Colon.

Fermentation of the polysaccharide components of fiber in the right colon results in the production of short chain fatty acids, acetic, propionic and butyric acids, and an attendant reduction in colonic pH[29]. Africans consuming a high-fiber diet were shown to have a fecal pH below 6.5, whereas those consuming a typical Western diet had more alkaline stools[30]. In another study, the average pH of Ugandan fecal samples was found to be 5.7, while that of English samples was 6.7[31].

The intestinal bacterial flora is pH-sensitive, and diet-related population differences in the composition of stool flora have been reported[32]. However, efforts to alter this variable by addition of fiber to the diet have not generally been successful[7]. Fecal flora composition may not necessarily reflect that of the right colon. Irrespective of the spectrum of bacterial species present, it is possible that fiber fermentation through alteration in colonic pH or redox may affect bacterial enzymatic activity so as to alter the colonic metabolism of steroids and other substances. This is significant since the secondary bile acids appear to have greater tumor promoting activity than the corresponding primary bile acids[20].

Enzymes responsible for bile acid metabolism have a pH optima of 6.5 or greater[33], and the extent of *in vitro* steroid degradation by fecal dehydrogenases and 7-deoxygenase is elevated at alkaline pH[34]. The reduced fecal steroid degradation in a population at low risk for colon cancer has been related to the acidity of their stools[31]. Similarly, the fiber analogue, lactulose, reduces cecal pH and effectively suppresses the metabolism of cholesterol to coprostanol, reduces bile acid dehydroxylation[35], and was shown to protect against large bowel tumor formation in an animal model[36].

Other metabolic processes in the colon are also affected by fiber fermentation. Cummings has discussed evidence suggesting that microbial fermentation of polysaccharide types of fiber also re-routes colonic nitrogen into bacterial protein synthesis and in so doing lowers colonic and portal venous blood

ammonia levels[29]. Reduction of intraluminal pH also tends to trap ammonium ion in the lumen. These effects may be important since Visek and colleagues have demonstrated that ammonia can induce changes in intestinal cells which favor tumor growth[37].

The effects of dietary fiber supplementation on fecal bacterial β-glucuronidase activity has also been studied. The enzyme releases active metabolites from glucuronide conjugates secreted by the liver which may then be further modified in the large intestine to reactive metabolites. Leguminous fiber significantly reduced β-glucuronidase activity in a recent animal study[38].

Finally, Bruce and co-workers have demonstrated the presence of volatile nitrosamines and non-volatile nitrosamides in human feces[39]. The production of these mutagenic N-nistroso compounds has been found to be in part dependent on pH, being elevated at pH 6.2-6.8[40]. Clearly more information is required on the effect of dietary fiber on the chemical environment of the colon and the activity of bacterial enzymes with regards to production of colonic substances with tumorigenic activity.

Effects of Fiber on Colonic Morphology

There is limited information on the effects of dietary fiber on colonic morphology. Vahouny and associates have reported that bile acid-binding fibers such as pectin can cause colonic cell destruction, disruption of the epithelial barrier and hemorrhage. These changes were attributed to the associated increase in the luminal bile acid concentration. In contrast, wheat bran and cellulose produced only an increase in goblet cell numbers[41]. Jacobs and White demonstrated that wheat bran increased both proximal and distal colonic cell mass. Whereas in the proximal colon this was associated with a decrease in cell turnover, in the distal colon, colonic cell synthesis as assessed by DNA incorporation of ^{3}H-thymidine was increased[42].

Conclusions

Dietary fiber undoubtably influences the colonic production and concentration of substances of putative significance in the etiology of large bowel neoplasms. Most of our current knowledge of the effects of fiber has been derived from studies of the composition and enzymatic activity of feces. Further information is required on the effects of dietary fiber in the right colon with particular reference to the metabolism and action of carcinogens and co-carcinogens. □

extensive references available upon request

THE FINAL WORD

Notes from the Front: A Perspective of Creativity

Harley Hahn 8T4

A human is the only form of organic matter that wears underwear.

Sometimes it is fun to stand back and ask what is it that distinguishes us from other forms of life. Skipping over four or five hundred thousand words of metaphysics, I assert that, aside from wearing underwear, humans are distinguished by their ability to be creative and by being able to focus awareness onto this creativity. And by creativity, I mean the act of producing that which requires thought and which did not previously exist.

Let me put this in perspective: we are all the time being creative; whenever we make a decision, choose something, have an idea. Creativity characterizes human thought, and hence, human existence. The geniuses and the artists of our world differ from their fellows not by what they do with their minds, but rather by how well they do it. Each one of us has a touch of Einstein and Beethoven in us. Unfortunately, a *touch* of creativity doesn't go very far.

A medical student is a person who would rather memorize a telephone book than learn the alphabet.

This suggests the importance of creativity: to allow us to organize our perceptions, compare them with previous patterns, and thus, to gain insight. Generally speaking, we use this insight to change either our outer environment, or for pleasure (which can be thought of as changing our inner environment).

The purpose of analysis is to divide an incomprehensible whole into a set of inconceivable parts.

We are alive for many years but most of the time we are usually not more than mildly creative. To explain this, let me propose a model of the mind.

In this model, the state of our mind is described by two

parameters: awareness and rationality. Awareness refers to the degree to which our attention is being focused outside of ourselves. We range from completely focussing our attention to the outside (for instance, if we are in danger), to focussing all of our energy inwards (autism). Sleeping is a time of autism.

Rationality also provides for a spectrum of possibilities, but in a more complicated manner. We can be highly rational, or we can be dream-like. (I will explain the use of the term "dream-like" below; I specifically have avoided the word "irrational" as this would imply a lack of sense and order.) When we are rational we are thinking according to a set of laws: the laws of logic. For example, an assertion is either true or false but not both.

When we are in a dream-like state we are operating by a different set of rules. These rules do not "make sense" because "sense" is a characteristic of rationality. If we are to understand this type of thinking, we must consider it differently. Let me compare dream thought to rational thought.

First off, dream thought is characterized by a preoccupation with concrete ideas while rational thought feeds off abstractions. Next, where rational thought groups ideas together that are bound by *logic*, dream thought groups ideas that are bound by *associations*.

Associations are internal, psychic connections between ideas. Seeing a ball may remind us of a game baseball. But associations are far richer than we suspect. The word "ball", for example, can also be used as a slang term for sexual intercourse. A friend of mine recently mentioned to me that thinking of the word "ball" made her think of "Saturday night".[1]

This example illustrates a number of characteristics of associations. First, ideas are bound by many associations to many other ideas with all sorts of cross-branching. Thus, not only may an idea lead us to several other ideas, but we may reach a particular idea by many different paths. We have all had the experience of having our thoughts return repeatedly to a particular idea.

A second characteristic of associations is that we find more of them connecting concrete ideas than connecting abstract ideas. One reason is that concrete ideas can be "pictured" with sense impressions, (particularly visual images), and with words; and both sense impressions and words are rich with associations.[2]

The example involving the word "ball" also illustrates that even the most innocent of psychic ideas often leads, by association, to sexual ideas. (In fact, some would have it that every idea is linked into our sexual ideational network.) We all know this to be true (although some of us choose not to accept it). To illustrate this to yourself, the next time you have a particular item that you find it difficult to memorize, link it in your mind with a vulgar, sexual idea. You will be astonished at how easy the item will be to remember.

But if ideas are linked with sexual items then they will also be involved with all the dynamics of internal sexual forces; with repression, with emotion, and with irresistable urges. This leads us to our last two characteristics of associations. They often *are* linked with sexual forces and as such, are subject to repression. For is it not that many artists speak of their creativity (which is intimately involved with their associations) as an irresistable, emotional force?

Most importantly, we see that associations exist *in our unconscious* and, for the most part, are unavailable to our conscious inspection.

Let us return now to our model which describes the state or our minds as a function of an awareness level and a rationality level.

We see that if the rationality level is closer to dream-like that to rational, we follow operating patterns that use concrete images and their rich network of associations. When we are thinking in this way we are free to let our psychic energy flow along association path, *unconstrained by logic*.

We condense many ideas onto a single, new idea. Conversely, we can also represent one idea in many ways. If we are unbound by logic, then we are free to employ our vast ideational networks to consider all manner of combinations of ideas, without requiring that they make sense. This allows us access to a vast region of our mind from which we are usually barred; a region in which information is stored and processed "illogically".

What sort of conditions allow us to set our rationality level towards the dream part of the spectrum? We can address this question by asking, what conditions allow us the freedom to think illogically? Clearly, conditions in which we feel safe. Since it is through logical thought that we control our environment, we must remain logical in times of danger.[3] But these times correspond exactly to the times when we are the most focussed outside ourselves. When we feel safe, we are free to set our awareness to be introspective and we are free to allow our thinking to become less rational and more dream-like. It is exactly at these times that we enjoy our best opportunities to be creative. This explains why it is so easy to be creative when we are relaxing in the bath, and why it is so difficult when we are playing hockey or surfing.

The last point I wish to make with respect to this model of our minds is to explain my use of the term "dream-like" as the counterpart of "rational". If we ask ourselves, when do we feel the safest, we would see that it is during sleep. In fact, as was mentioned earlier, sleep is an autistic activity; that is, all our attention is focussed inwards. As Freud explains in his *Interpretation of Dreams*, the world of sleep is characterized by thinking patterns that are foreign to everyday life. In fact, it is

[1] But she wouldn't tell me if she meant last Saturday night or next Saturday night.

[2] This is to be expected when we realize that information coming from the outside world is usually mediated as an image or other sense impression, while outgoing information usually takes the form of words.

[3] One might argue that since in times of danger we sometimes act stupidly, thus we are not acting logically. This argument confuses judgement with patterns of thinking. Following a logical pattern of thinking does not imply good judgement.

these patterns, the dream-like state, that our model takes as the counterpart to the rational state.

It is interesting to notice that indeed, we are the most creative when we are asleep; that is, when we are purely operating under the authority of dream thinking. However, the products of this thinking (dreams) are useful only in a personal sense. Clearly, if we are to use our creativity to be productive in a pragmatic sense, we must set our awareness at a higher level than that of sleep; and we must set our rationality level to include at least a small amount of logical thought. I will return to these points later.

I am most creative when I have work to do.

Now that we have explored the regions of creativity it is fair to ask: How can we induce such a state? As the above observation implies, we do not always have control over our ability to create. Often, we seem to develop an urge to create at exactly the time that we are faced with dull, difficult work.

On the other hand, we may have the opposite problem. Consider this description, by Max Shulman, of a college student trying to compose an English theme, due on a Friday morning:

> Not until six o'clock Thursday evening did I get to the theme. I set two fountain pens, a bottle of ink, an eraser, three pencils, a dictionary, a thesaurus, and a ream of fresh white paper on my desk. I adjusted the goose-neck lamp for minimum eyestrain. I pulled up a straight-back chair. I opened the window. I filled a pitcher with water, I took my phone off the hook. Then I sat down and drew isoceles triangles for two hours.

Learning to control our creativity is surely a valuable skill. Our first clue can come from our understanding of the conditions under which creativity thrives. If we want to be creative, we must make sure that we are in a conductive environment. It must be such that we feel safe enough so that we are not forced to set our attention too far away from the internal side of the spectrum. Remembering that our minds constantly interpret stimuli to see if they pose a threat to us, we are "safest" when we have minimized distractions of all kinds. We should also be relaxed and comfortable. This allows us to allot more of our attention inwards and hence, to set our pattern of thinking to be more dream-like than rational.

There are well-known stories of creative insight (for example, Archimedes in the bath) that can be understood in terms of this model. Conditions such as J have just described give birth to what the philosopher Michael Dan calls the 'Aha' Phenomenon: the appearance of spontaneous insight.

But to be creative in the grand sense requires more than the appropriate levels of attention and rationality. We must have a significant background of knowledge on which to paint our discoveries, and we must be suitably motivated.

The importance of knowledge is often overlooked. But it is impossible to make a great discovery unless one understands and *appreciates* the work that has already been done in the area. This suggests that to learn to be creative we must learn a certain quantity of facts. There is no getting around this. Moreover, we must come to appreciate the importance of these facts. We must build up patterns in our minds upon which our creativity can dance. Truly, if you don't have a basket, you won't find anything to put in it.

The only good vegetable is a dead vegetable.

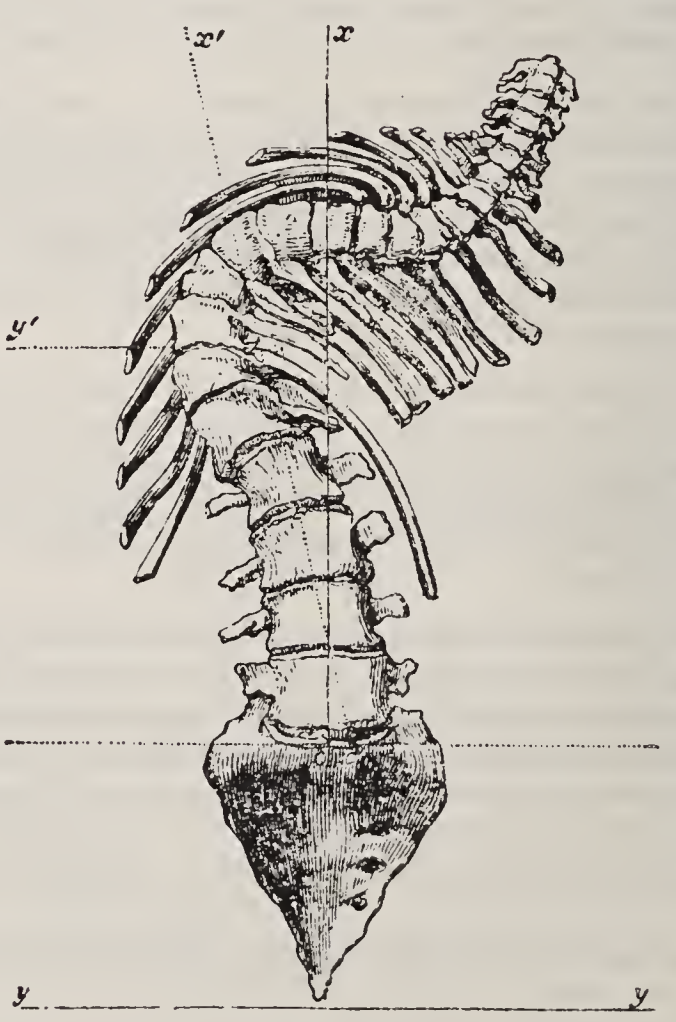
Unlike vegetables, ideas are good only when they are alive — that is, infused with psychic energy. It is in providing this psychic energy that motivation induces creativity. Motivation comes in several flavors: we may be interested in solving a particular problem or we may exhibit a general curiosity about what we see around us. The way to think about it is that creative people always have a good-sized amount of curiosity in stock so that they can fill any particular motivational need as it arises.

To be creative, we must cultivate the constant posture of questioning; and we would have it that our questions arise out of wonder and awe rather than out of cynicism and insecurity. We must encourage others to ask why and we must constantly do so ourselves.

In a hospital, it often seems that the only people allowed to wear white are those who have never given birth to an original idea.

Truly, by being creative we distinguish ourselves as a species. At the end of this article in this issue of the *Medical Journal*, Dr. Salter urges medical students and doctors to "explore where there is no path". If we are to do so then we must exploit the treasure of curiosity that, as human beings, is our birthright.

Today, human creativity is the cutting edge of evolution. We must cultivate our garden. □



Reproduced from Researches into the Pathology and Treatment of Deformities in the Human Body *by John Bishop, F.R.C.S., Highley and Son, London, 1852. Held in the University of Toronto, Thomas Fisher Rare Book Library.*

MEDICAL OFFICER TRAINING PLAN

The Medical Officer Training Plan provides for:

— Up to three years' academic tuition.
— Financial subsidization during your internship.
— You receive a monthly salary from the time of enrolment until graduation. Thereafter you are paid the appropriate Medical Officer salary.
— An annual allowance for the purchase of medical books and instruments.
— A substantial allowance for the initial purchase of uniforms.
— 30 days' holiday each year, with pay.
— Medical and dental care.
— Other benefits and privileges of the Service and a commissioned status.
— A guaranteed position of respect and a good starting salary.

For more information, visit the Canadian Forces Recruiting Centre Toronto, at 4900 Yonge Street, Willowdale (near Sheppard Avenue subway station), or telephone 224-4015

THERE'S NO LIFE LIKE IT
THE CANADIAN ARMED FORCES

Canada

Patrons

Many of the individuals on this page are our teachers; others simply admirers. All have given generously, not only financially, but as persons deeply committed to medical education, and for this we are truly grateful.

Dr. P.W. Alberti, Toronto
Dr. E.C. Allen, Toronto
Dr. K.A. Ally, Agincourt
Dr. G. Harvey Anderson, Toronto
Dr. Crawford S. Anglin, Toronto
Dr. John D. Armstrong, Willowdale
Dr. Mary Jane Ashley, Toronto
Dr. Michael A. Baker, Toronto
Dr. Colin E. Bayliss, Toronto
Dr. Patrick F. Beirne, Toronto
Dr. R.J. Benzie, Toronto
Dr. Sam Berger, Downsview
Dr. John A. Beswick, West Hill
Dr. Barbara Jane Blake, Toronto
Dr. Robert S. Braiden, Toronto
Dr. Charles B. Brown, Toronto
Dr. Peter J. Brueckner, Don Mills
Dr. Martin B. Buckspan, Toronto
Dr. Gerard Noel Burrow, Toronto
Dr. David S. Byers, Toronto
Dr. Ross Cameron, Toronto
Dr. Lorie E. Cappe, Toronto
Mrs. Mary Casey, Toronto
Dr. Daniel C. Cattran, Toronto
Dr. Anthony Cecutti, Don Mills
Dr. Albert T. Cheskes, Toronto
Dr. Joshua J. Chesnie, Toronto
Dr. Herbert M. Chinyanga, Toronto
Dr. Robert James Chisholm, Toronto
Dr. Robert A. Cleghorn, Toronto
Dr. Max Mark Cohen, Toronto
Dr. Sheila Gale Cohen, Willowdale
Dr. Richard Harold Comisarow, Toronto
Dr. John S. Crawford, Toronto
Dr. Donald J. Currie, Toronto
Dr. Derek A. Davidson, Weston
Dr. Yvonne E. DeBuda, Toronto
Dr. Robert B. Disenhouse, Willowdale
Dr. James Duffin, Toronto
Dr. Emmanuel Farber, Toronto
Dr. Shim Felsen, Willowdale
Dr. Ronald Storey Fenton, Toronto
Dr. James Kenneth W. Ferguson, Thornhill
Dr. John M. Finlay, Toronto
Dr. J.F. Ross Fleming, Toronto
Dr. Rodney S. Fowler, Toronto
Dr. William Hedley Francombe, Toronto
Dr. Robert W. Francis, Toronto
Dr. Arthur E. Franklin, Toronto
Dr. Arnis Freiberg, Toronto
Dr. George L.A. From
Dr. A. Geisler, Mississauga
Dr. Richard M. Gladstone, Willowdale
Dr. David M. Goldberg, Toronto
Dr. Eudice Goldberg, Toronto
Dr. Melvyn Goldberg, Toronto
Dr. Irvin Gollish, Toronto
Dr. Patricia Goodhall-Gunn, Toronto
Dr. Duncan A. Gordon, Toronto
Dr. Allan E. Gross, Toronto
Dr. L.F.L. Grover, Islington, Ont.
Dr. A.L. Halpern, Mamaroneck, N.Y.
Dr. Edward S. Hamer, Toronto
Dr. Gordon D. Hardacre, Toronto
Dr. Ian J. Harrington, Toronto
Dr. Gerald D. Hart, Toronto
Dr. Barbara E. Hazlett, Toronto
Dr. Gerald Archibald Heasman, Toronto
Dr. Robert Dargue Henderson, Toronto
Dr. Robert Carey Hicks, Toronto
Dr. H.P.M. Higgins, Toronto
Dr. F. Marguerite Hill, Toronto
Dr. Charles H. Hollenberg, Toronto
Dr. Alan R. Hudson, Toronto
Dr. Robin P. Humphreys, Toronto
Dr. M.A. Hutcheon, Toronto
Dr. Robert Hyland, Toronto
Dr. Aden C. Irwin, Halifax, N.S.
Dr. Mary V. Jackson, Toronto
Dr. Frederick Albert Jaffe, Toronto
Dr. Donald Philip Jones, Toronto
Dr. John P. Kostiuk, Toronto
Dr. James Hunter Kerr, Toronto
Dr. Edward C. Keystone, Toronto
Dr. Jay Stephen Keystone, Toronto
Dr. Bernard Langer, Toronto
Dr. Arthur Eugene LeBlanc, Toronto
Dr. Wolf-Dietrich Leers, Toronto
Dr. Jack Leitch, Toronto
Dr. Daniel Levy, Hamilton
Dr. Frances Levy, Hamilton
Mr. Sidney Liswood, Toronto
Dr. E. Llewellyn-Thomas, Toronto
Dr. Lynn F.W. Loach, Toronto
Dr. Frederick H. Lowy, Toronto
Dr. John R. Lundon, Toronto
Dr. Ross MacKay, Toronto
Dr. Robert Lee Mackenzie, Toronto
Dr. S.M. MacLeod, Toronto
Dr. Ian MacNab, Toronto
Dr. Aaron Malkin, Toronto
Dr. Constantine Malkin, Toronto
Dr. Joseph T. Marotta, Don Mills
Dr. A. Bruce Marshall, St. Marys, Ont.
Dr. Victor W. Marshall, Toronto
Dr. Ray Dennis Martin, Toronto
Dr. Benjamin Massouda, Downsview
Dr. Nancy H. McKee, Toronto
Dr. Raymond M. McKeown, North Bend, Oregon
Dr. Rosemary Meier, Toronto
Dr. Peter G. Mingie, Toronto
Dr. Mario A. Moscarello, Toronto
Dr. Keith L. Moore
Dr. James F. Murray, Don Mills
Dr. William Ross Nelson, Toronto
Dr. D.G. Oreopoulos, Toronto
Dr. Frederick R. Papsin, Toronto
Dr. Thomas A. Patterson, Toronto
Dr. Gordon Allan Pengelly, Toronto
Dr. Richard G. Perrin, Toronto
Dr. Walter J. Peters, Toronto
Dr. Mel E. Petersiel, Toronto
Dr. Burns Plewes, Toronto
Dr. Kathleen I. Pritchard
Dr. C. Phillips Rance, Toronto
Ms. Joanne Ratz, Toronto
Dr. William J. Reynolds, Toronto
Dr. Kenneth V. Robb, Toronto
Dr. Alexander Roberts, Toronto
Dr. Daniel A.K. Roncari, Toronto
Dr. Robert B. Salter, Toronto
Dr. Michael K. Sarin, Toronto
Dr. Edward Sellers, Toronto
Dr. Edward M. Sellers, Toronto
Dr. John S. Senn, Toronto
Dr. David L. Shaul, Toronto
Dr. Robert H. Sheppard, Toronto
Dr. Isaac Shlesser, Toronto
Dr. Jack Shuber, Toronto
Dr. Kenneth H. Shumak, Toronto
Dr. Daniel Silver, Toronto
Dr. Bernard Sliverman, Toronto
Dr. Ruth Sky, Toronto
Dr. Ann Whyte Smith, Mississauga
Dr. J. Donald Smith, Mississauga
Mr. J. Douglas Snedden, Toronto
Dr. G.E. Douglas Snell, Toronto
Dr. Frank Sommers, Toronto
Dr. Paul D. Steinhauer, Toronto
Dr. Donald A. Stewart, Toronto
Dr. Robert M. Stone, Toronto
Dr. Hans D. Strauss, Toronto
Dr. Lorne Marvin Tarshis, Toronto
Dr. Ronald Taylor, Toronto
Dr. Sallie Jean Teasdale, Toronto
Dr. J.A. Peter Turner, Toronto
Dr. Joan M. Vale, Toronto
Dr. Daniel G. Vaughan, San Jose, Calif.
Dr. Hillar Vellend, Toronto
Dr. J.P. Waddell, Toronto
Dr. Paul G. Walfish, Toronto
Dr. R. Kirk Weber, Toronto
Dr. Gary D. Webb, Toronto
Dr. Richard D. Weisel, Toronto
Dr. Gordon F. Whitmore, Toronto
Mr. Harry Whittaker, Toronto
Dr. Robert H. Wilkinson, Toronto
Dr. Douglas R. Wilson, Toronto
Dr. George Edward Wodehouse, Toronto
Dr. and Mrs. M.S. Wolochow, Richmond, B.C.
Dr. Colin R. Woolf, Toronto
Dr. Walter Zingg, Toronto
Dr. Ronald Melvin Zucker, Toronto
Governing Council, University of Toronto
CIBA-GEIGY Canada Ltd.
Novopharm Ltd.
Ortho Pharmaceuticals Ltd.

The University of Toronto Medical Journal is published four times a year with the generous assistance of the Medical Society, University of Toronto Faculty of Medicine. The text was set by Media I Graphics Ltd., Downsview, Ontario, using the latest in computer technology. Printing was by Letter Perfect Press, Downsview, using a good old fashioned ink. General Articles are contributed by undergraduate medical students at the University of Toronto, and Guest Articles by distinguished members of the Toronto medical teaching community. Persons or organizations wishing to advertise in the Journal should contact Mr. Michael Bazos, Advertising Director, University of Toronto Medical Journal, Medical Sciences Building, Room 2141, University of Toronto, Toronto, Ontario M5S 1A8. Subscription rates are $10 per year.

ORTHO-NOVUM* 1/50

NORETHINDRONE
AND MESTRANOL
TABLETS

Indication: Conception control.

Contraindications: Thrombophlebitis, thromboembolic disorders, cerebral vascular disease, coronary thrombosis, or a history of these conditions; significant liver dysfunction or disease; history of cholestatic jaundice; known or suspected malignancy of the breast or genital tract, or history of these conditions; known or suspected estrogen-dependent neoplasia; undiagnosed abnormal vaginal bleeding; known or suspected pregnancy; during the period a mother is breast-feeding an infant; any ocular lesion associated with ophthalmic vascular disease such as partial or complete loss of vision, defect in visual fields or diplopia, classical migraine.

Warnings: Discontinue medication at the earliest manifestations of: A. Thromboembolic disorders. B. Visual disturbances including; (i) gradual or sudden, partial or complete loss of vision; (ii) proptosis or diplopia; (iii) onset or aggravation of migraine; (iv) papilledema; (v) opthalmic vascular lesions. C. Development of headache which is recurrent; persistent or severe and undiagnosed. D. Psychiatric disturbances. Rule out pregnancy in patients who have missed a menstrual period. Patients with epilepsy, diabetes mellitus, asthma and cardiac or renal dysfunction require careful observation. In women with predisposing factors for cardiovascular disease, oral contraceptives have been reported as an additional risk. After the age of 40 years, for purposes of fertility control, oral contraceptives should be considered only in exceptional circumstances, and when the risk/benefit ratio has been carefully weighed by both the physician and the patient.

Precautions: Before use, take a thorough history, and perform a thorough physical examination including a blood pressure determination and examination of breasts, liver and pelvic organs. A Pap Smear should be taken. First follow-up examination is at 6 months, and at least yearly thereafter, including all tests initially performed. Women with a history of jaundice should be prescribed oral contraceptives under close observation. If there is a history of cholestatic jaundice, especially during pregnancy, other methods of contraception should be prescribed. The development of severe generalized pruritus or icterus requires that the medication be withdrawn until the problem is resolved. If jaundice is cholestatic in type, do not resume oral contraceptive administration. Changes in composition of bile and the appearance of cholesterol gallstones have been reported in women taking oral contraceptives. Hepatic neoplasms and nodular hyperplasias or hamartomas have been reported in oral contraceptive users. Although these tumors are uncommon, they have caused fatal intra-abdominal hemorrhage and should be considered in women presenting with acute abdominal pain, an abdominal mass or evidence of intra-abdominal bleeding. Patients with essential hypertension may be prescribed oral contraceptives under close supervision. If a significant blood pressure elevation in previously normotensive or hypertensive subjects occurs at any time, cessation of medication is indicated. Diabetic patients or those with a family history of diabetes should be observed closely. Latent diabetics who can be kept under close supervision may be prescribed oral contraceptives. Young patients with overt diabetes whose disease is of recent origin, well-controlled and not associated with hypertension or other signs of vascular disease should be closely observed. In metabolic or endocrine diseases and when calcium and phosphorus metabolism is abnormal, careful clinical evaluation should precede medication. The risk of complications due to adrenocortical insufficiency appears to be minimal with oral contraceptive therapy. Estrogen-progestogen combinations may cause an increase in plasma lipoproteins and should be administered with caution to women known to have preexistent hyperlipoproteinemia. Use special judgement in prescribing oral contraceptives to women with fibrocystic breast disease. Persistent irregular vaginal bleeding requires investigation to exclude the possibility of pregnancy or neoplasm. Observe patients with fibroids carefully. Sudden enlargement, pain or tenderness of uterine fibroids require discontinuation of medication. Assess adolescent patients for adequate skeletal development prior to medication, since oral contraceptives may accelerate epiphyseal closure. Oral contraceptive therapy may mask the onset of the climacteric. In general, women in the later reproductive years gradually assume an increasing risk of circulatory and metabolic complications, especially at age 35 to 40. Shorter duration of oral contraceptive use, and avoidance of cigarette smoking is advisable. Patients with a history of emotional disturbances, especially the depressive type, are more prone to have a recurrence. In cases of serious recurrence, the medication should be discontinued in favour of a non-hormonal method of contraception for a trial period to determine if the symptom is therapy related. The following laboratory tests should not be considered reliable unless oral contraceptive therapy has been discontinued for 2 to 4 months: liver function tests; coagulation tests; thyroid function tests; adrenocortical function tests; reproductive endocrine profile changes; and other tests involving phospholipids, triglycerides, serum folate, tryptophan metabolism, and serum glucose. Advise pathologists of oral contraceptive therapy when specimens are submitted for examination. After discontinuing oral contraceptives, the patient should use an alternate non-hormonal method of conception control and await the resumption of normal ovulatory cycles before attempting to become pregnant. Women with a history of oligomenorrhea or secondary amenorrhea or women with irregular cycles may remain anovulatory or become amenorrheic following estrogen-progestogen combination therapy. Amenorrhea, especially if associated with breast secretion that continues for 6 months or more after withdrawal, warrants a careful assessment of hypothalamic-pituitary function. Fetal abnormalities have occured in the offspring of women who have taken progestogens and/or estrogens during pregnancy. The safety of oral contraceptives in pregnancy has not been demonstrated. Rule out pregnancy before initiating or continuing the contraceptive regimen. Always consider pregnancy if withdrawal bleeding does not occur. Retrospective studies have reported an increased risk of post-surgery thromboembolic complication in oral contraceptive users. Therapy should be discontinued at least 1 month prior to elective surgery and not resumed until at least 2 weeks after hospital discharge following surgery associated with an increased risk of thromboembolism. A reduced efficacy and increased incidence of breakthrough bleeding have been reported in oral contraceptive users treated concomitantly with barbiturates, rifampicin, phenylbutazone, phenytoin or ampicillin. Protracted vomiting and/or diarrhea may decrease the absorption and effectiveness of oral contraceptives. Should these occur, an additional method of contraception should be recommended for the remainder of the cycle.

An increased risk of the following seriously adverse reactions has been associated with the use of oral contraceptives; thrombophlebitis; pulmonary embolism; mesenteric thrombosis; neuro-ocular lesions; myocardial infarction; cerebral thrombosis; cerebral hemorrhage; hypertension; benign hepatic tumors; gall bladder disease, congenital anomalies. The following adverse reactions have also been reported in patients receiving oral contraceptives: nausea and vomiting; gastrointestinal symptoms; breakthrough bleeding and spotting; change in menstrual flow; dysmenorrhea; amenorrhea; temporary infertility; edema; chloasma; melasma; breast changes; weight change; endocervical hyperplasias; diminution in lactation when given immediately postpartum; cholestatic jaundice; migraine; increased size of uterine leiomyomata; rash; mental depression; reduced carbohydrate tolerance; vaginal candidiasis; premenstrual-like syndrome; intolerance to contact lens; change in corneal curvature; cataracts; libido change; chorea; appetite change; cystitis-like syndrome; headache; nervousness; dizziness; hirsutism; loss of scalp hair; erythema multiforme; erythema nodosum; hemorrhagic eruption; vaginitis; porphyria; impaired renal function.

Dosage: - 21 day regimen: 1 tablet daily for 21 days, followed by 7 days without medication.
Cyclic administration.
- 28 day regimen: 1 tablet daily for 21 days, followed by 7 inert green tablets.
Continuous administration.

Supplied: ORTHO 1/35: each peach tablet engraved on both sides with "ORTHO 1" contains 1.0 mg norethindrone and 35 mcg ethinyl estradiol. ORTHO-NOVUM 1/50: each yellow tablet engraved on both sides with "ORTHO 1" contains 1.0 mg norethindrone and 50 mcg mestranol. In the 28-day regimens the green tablets contain inert ingredients. Available in a 21-day or 28-day DIALPAK* Tablet Dispenser.

References: 1. Knopp, R.H., Walden, C.E., Wahl, P.W., Hoover, J.J.: "Effects of Oral Contraception on Lipoprotein, Triglyceride and Cholesterol: Relationships to Estrogen and Progestin Potency"; American Journal of Obstetrics and Gynecology, March 1982.
2. Wynn, V., Niththyananthan, R.: "The Effect of Progestins in Combined Oral Contraceptives on Serum Lipids with Special Reference to High-Density Lipoproteins"; American Journal of Obstetrics and Gynecology, March 1982.
3. Spellacy, W.N.: "Carbohydrate Metabolism During Estrogen, Progestogen and Low-Dose Oral Contraceptive Treatment"; American Journal of Obstetrics and Gynecology, March 1982.
4. Data on file, Ortho Pharmaceutical (Canada) Ltd.

ORTHO PHARMACEUTICAL
(CANADA) LTD.
Don Mills, Ontario

ORTHO

*Trademark © Copyright 1982, Ortho Pharmaceutical (Canada) Ltd.

PAAB
CCPP

ORTHO* 1/35

NORETHINORONE AND
ETHINYL ESTRADIOL
TABLETS

The CIBA Collection of

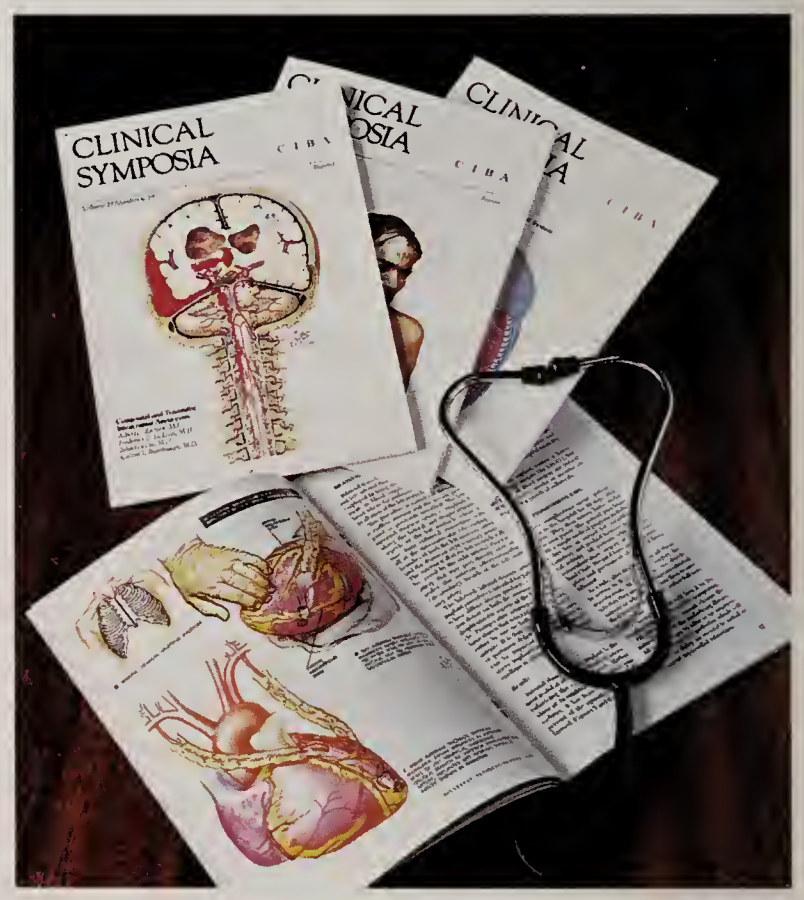
MEDICAL ILLUSTRATIONS

by Dr. Frank H. Netter

Seven volumes *(9 books)* that present human anatomy, physiology and pathophysiology, through comprehensive medical texts and the superb full-colour illustrations of the renowned artist-physician, Dr. Frank Netter.

The nine available titles are:

Nervous System – *Volume 1*
Reproductive System – *Volume 2*
Upper Digestive System – *Volume 3, Part 1*
Lower Digestive System – *Volume 3, Part 2*
Liver, Biliary Tract and Pancreas – *Volume 3, Part 3*
Endocrine System – *Volume 4*
Heart – *Volume 5*
Kidneys, Ureters and Urinary Bladder – *Volume 6*
Respiratory System – *Volume 7*



Clinical Symposia Reprints

To complete or add to your medical reference library. More than 70 editions that have been published over the years are available in their original format with all the full-coloured illustrations. Many are being introduced into Canada for the first time. Please note they contain *no advertising.*

CIBA Medical Slides

Our 35mm Kodachrome slides present over 3,000 of the medical illustrations that are featured in The CIBA Collection of Medical Illustrations and Clinical Symposia. Through the use of our codes and listing, each slide can be matched up with the original illustration.

C I B A

Mississauga, Ontario L5N 2W5

C-1187